Influence of Pancreas Transplantation on Cardiorespiratory Reflexes, Nerve Conduction, and Mortality in Diabetes Mellitus

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Cardiorespiratory reflexes (CRR) were studied by measuring heart-rate variation during 6 breaths/min respiration and a Valsalva maneuver in 232 insulin-dependent diabetic subjects. Abnormalities were found in 175 patients. During a 7-yr follow-up, 41 (23.4%) patients with abnormal and 2 (3.5%) with normal CRR tests died. The mortality rates of diabetic patients with abnormal autonomic function tests were 17% at 2.5 yr, 33% at 5 yr, and 40% at 7 yr, significantly higher ($P < 0.002$) than in patients with normal tests (rates of 4.6, 4.6, and 13.8% at the respective intervals). Nerve conduction studies (NCS) were indicative of somatic neuropathy in 148 of 205 patients. Mortality rates were higher in patients with abnormal NCS than in those with normal results ($P < 0.025$). Among patients with abnormal autonomic function, patients with a functioning pancreas transplantation (PTx) had better survival rates than patients with a failed PTx ($P < 0.005$) and, on long-term follow-up, better rates than patients without PTx. Similar results were found comparing the same group of patients who had abnormal NCS. *Diabetes* 39:802–806, 1990

Diabetes mellitus may adversely affect the autonomic nervous system in virtually every organ, but the effects are more easily detectable in the cardiovascular system (1). Abnormal results on cardiovascular function tests have been reported in up to 75% of unselected diabetic patients (2–7), in several cases at the time diabetes was first diagnosed (8,9). This is much greater than the incidence of symptoms of autonomic neuropathy (reported with variable frequency up to 27%; 8,10) suggests (1,7). Neurophysiological investigation of autonomic function is important in the evaluation of diabetic patients, because the results of these tests often do not correlate with symptoms of autonomic dysfunction or results of the somatic sensorimotor nerve tests (7). Moreover, abnormalities of cardiovascular tests are generally associated with a high frequency of sudden death (11) and a mortality ratio of >50% after 5 yr, considerably higher than the 11% found in the general diabetic population (12,13).

We investigated mortality in a large group of type I (insulin-dependent) diabetic patients who were evaluated with cardiorespiratory reflex (CRR) tests and followed for between 1 and 7 yr. This prospective study evaluated the usefulness of CRR tests as predictors of prognosis and mortality in diabetes mellitus and assessed the influence of a normoglycemic state achieved by a functioning pancreas transplantation (PTx).

RESEARCH DESIGN AND METHODS

Information was collected from 232 patients with type I diabetes mellitus who were studied for autonomic function in our laboratory between August 1980 and December 1986. The subjects were 94 men and 138 women (mean ± SD age 33.2 ± 9.2 yr) who had had diabetes for 20.2 ± 9.1 yr at entry into the cohort. Of these patients, 137 received PTx after the initial evaluation. We determined the number of patients who died before 31 December 1987 and the cause of death. The duration of follow-up varied from 12 to 88 mo, with 12 patients followed for >7 yr. The pancreas graft was functioning in 53 cases in December 1987 or at the time of death. The transplant failed within <3 mo in 65 patients and at intermediate times in the remaining 19 patients.

CRR tests were performed as previously described (7). Heart rate was monitored continuously by a tachygraph during deep breathing at 6 breaths/min. The mean difference between the highest heart rate during inspiration and the lowest rate during respiration for seven consecutive breathing cycles was called the ΔR6. Heart-rate variations were also recorded during a Valsalva maneuver, maintaining a pressure of 40 mmHg for 10 s. The highest rate during the maneuver divided by the lowest rate within 30 s after the

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maneuver was called the Valsalva ratio. Normal limits were established for each age decade as the 95th percentile of values obtained from control subjects studied in our laboratory (7).

Peripheral sensorimotor neuropathy was assessed by nerve conduction studies (NCS). Motor nerve conduction was measured for one ulnar, median, peroneal, and tibial nerve. Orthodromic sensory nerve conduction was measured in one median and sural nerve. Results were considered abnormal when they were below the normal limits for our laboratory in at least two nerves.

Survival estimates were calculated with the life-table method, and their differences were analyzed statistically by the log-rank test. The effects of several variables on survival were analyzed with Cox proportional-hazards regression with BMDP statistical software. Comparisons between groups were made with *t* tests and χ^2-tests. All tests of significance were two sided.

RESULTS

Cardiorespiratory reflexes and mortality. Both CRR tests were abnormal in 152 patients, only one test was abnormal in 23 patients, and both tests were within the normal range in 57 patients. Demographic characteristics of groups with normal and abnormal results are shown in Table 1. There were statistically significant differences in age, duration of diabetes, results of CRR tests, and degree of sensorimotor neuropathy between patients with normal and abnormal tests. Duration of follow-up was similar in the two groups.

In the cohort of 232 patients, there were 43 deaths (18.5%) during the observation period. The causes of death were myocardial infarction in 6 patients, cardiac arrest in 4 patients, heart failure in 2 patients, pulmonary failure or distress in 4 patients, liver failure in 4 patients, kidney failure in 4 patients, and hyperglycemia, hypoglycemic coma, pulmonary embolism, lymphoma, anaphylactic shock, viral infection, and drug overdose each in 1 patient. Sudden death of unknown cause occurred in 2 patients. No reliable information could be obtained on the cause of death in 10 patients.

Comparisons of patients who died with those who survived showed no differences in age or duration of diabetes at entry into the study but did show significantly lower values for the CRR tests ($P < 0.01$). Only 2 patients with normal test results died, another had one abnormal test, and both tests were abnormal in 40 patients. Calculated mortality rates were 17% at 2.5 yr, 33% at 5 yr, and 40% at 7 yr in patients with abnormal CRR tests and 4.6, 4.6, and 13.8% at the respective intervals for patients with normal test results. The survival curves for the groups of patients with normal and abnormal CRR tests are shown in Fig. 1. Survival was significantly lower for patients with abnormal tests ($P < 0.002$). Survival was not significantly associated with sex, age, or duration of diabetes at entry into the study.

TABLE 1
Characteristics of diabetic patients

	Cardiorespiratory reflex tests	
	Normal	Abnormal
n (F/M)	28/29	110/65
Age (yr)	28.3 ± 7.8	34.8 ± 9.1*
Duration of diabetes (yr)	13.1 ± 8.3	22.6 ± 8.1*
Follow-up (mo)	40.8 ± 25.4	39.7 ± 25.2
Abnormal nerve conduction studies (*n*)	20 (38.6)	158 (90.5)†
ΔR6	25.7 ± 8.7	5.4 ± 5.1*
Valsalva ratio	1.87 ± 0.34	1.19 ± 0.20*

Values are means ± SD. Numbers in parentheses are percentages. ΔR6, average difference between highest heart rate during inspiration and lowest heart rate during respiration for 7 consecutive breathing cycles. Valsalva ratio, highest heart rate during Valsalva maneuver divided by the lowest rate within 30 s after maneuver.
*$P < 0.001$; †$P < 0.05$.

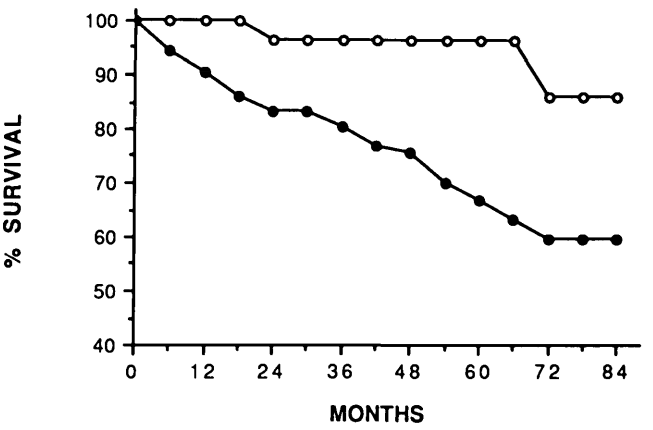

FIG. 1. Survival curves for diabetic patients with (●) and without (○) abnormalities in cardiorespiratory reflex tests.

Nerve conduction and mortality. Evidence of somatic neuropathy, demonstrated by abnormalities in at least two nerves in NCS, was found in 148 of 205 patients who had a complete study. The results of CRR tests and NCS were concurrent, either normal or abnormal, in 85% of patients. Of the 205 patients, 37 (18%) patients died by the study day, 4 patients with normal and 33 patients with abnormal NCS. The survival curves of patients with normal or abnormal NCS were different but with lesser significance ($P < 0.025$) than the comparison based on CRR tests in Fig. 1 (Fig. 2). Calculated mortality rates were 16.6% at 2.5 yr and 34% at 5 yr for the 148 patients with abnormal NCS and 5.6% at 2.5 yr and 11.2% at 5 yr for the 57 patients with normal NCS.

Influence of PTx. To assess the influence of PTx, we compared the patients with a functioning graft to those whose grafts failed before 3 mo. The 19 patients with graft failure at various intervals >3 mo are not included in the comparisons. There were no statistically significant differences between these groups regarding age, duration of diabetes, or degree of neuropathy (Table 2). Five of the 53 patients with a functioning PTx died. In 2 patients (40% of the deaths), death could be attributed to complications of either the surgical procedure or the consequent immunosuppressive treatment. None of the 5 patients had normal CRR tests. Of the 65 patients with a failed PTx, 22 patients died, 9 patients (41%) from causes related to PTx; 1 of these patients had normal CRR tests. The survival curves, considering only patients with abnormal CRR tests (43 with functioning PTx, 55 with failed PTx), showed a clear difference ($P < 0.005$) between the outcome of both groups, either considering all the deceased patients (Fig. 3) or excluding those whose death

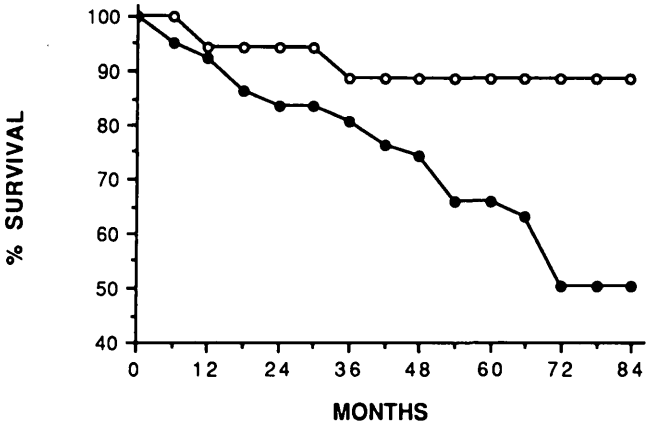

FIG. 2. Survival curves for diabetic patients with (●) and without (○) abnormalities in nerve conduction studies.

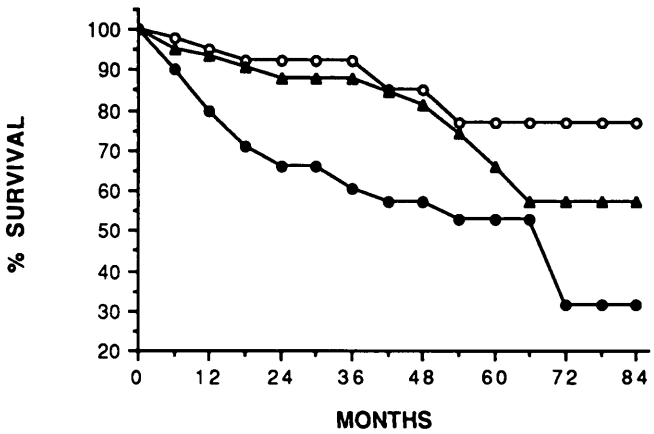

FIG. 3. Survival curves for diabetic patients with abnormalities in cardiorespiratory reflex tests who had functioning pancreas transplantation (PTx; ○), failed PTx (●), or no PTx (▲).

was related to complications of surgery or immunosuppression.

Of the 95 patients without a PTx, 15 patients (15.8%) died, only 1 with normal CRR results. Despite the risk intrinsic to surgery and immunosuppression, survival of patients with a functioning PTx and abnormal CRR was not significantly different ($P < 0.1$) and, in fact, was better on the prolonged follow-up than the survival curve of the 62 patients without a PTx and abnormal CRR (Fig. 3). Similar results were found when comparing all patients with abnormal NCS from each of the three PTx groups (Fig. 4). Patients with a functioning PTx had a better survival rate than patients with a failed PTx ($P < 0.02$) and without a PTx ($P < 0.05$).

DISCUSSION

The presence of autonomic dysfunction is most commonly assessed by testing cardiovascular reflex responses. With these methods, the prevalence of autonomic dysfunction in diabetic patients varies from 20 to 75% (2–7). The proportion of abnormal CRR tests in the patients included in this study (75%) is similar to the proportion found in a larger series of 417 patients previously reported (7). This high rate of abnormalities is probably due to the characteristics of the population studied, many of the patients being candidates for different therapeutic trials (including PTx), having diabetes of long duration, and manifesting secondary complications.

The natural history of diabetic autonomic neuropathy is of slow progression. CRR test results are abnormal in a large proportion of patients with symptoms of autonomic neuropathy and in many who deny symptoms (7–9,14). Once CRR function is abnormal, it remains so or deteriorates in time (4,14). When diabetic patients eventually become aware of autonomic symptoms, impairment may be advanced, and presumably the prognosis is worse. Ewing et al. (12,13) followed patients with symptoms of autonomic neuropathy and abnormal cardiovascular tests and found a mortality rate of 44% at 2.5 yr and 56% at 5 yr, considerably higher than the 6 and 11% rates at the same time points in a general diabetic population. Watkins and Mackay (14) studied heart-rate variation during deep breathing and found that 27% of 64 diabetic patients with abnormal test results died during a 5-yr follow-up; 4 patients died suddenly. The existence of gastroparesis has also been shown to be accompanied by high mortality (35% in 3 yr; 15). These results are in agreement with our findings of mortality rates of 17% at 2.5 yr and 33% at 5 yr among the 175 patients with abnormal CRR tests. Of these patients, 41 died during the 7-yr follow-up, whereas only 2 of 57 patients with normal tests died. These observations confirm that diabetic patients with abnormal CRR tests have a higher mortality risk than patients with normal tests.

The positive relationship between autonomic and somatic nerve abnormalities, shown by good correlations between CRR and sensorimotor nerve conduction (7,16), favors the

TABLE 2
Characteristics of groups of diabetic patients according to pancreas-transplantation (PTx) status

	Functioning PTx	Failed PTx	No PTx
n (F/M)	36/17	41/24	46/49
Age (yr)	31.7 ± 6.2	32.3 ± 6.3	35.1 ± 12.1
Duration of diabetes (yr)	20.5 ± 6.4	21.1 ± 6.7	19.4 ± 12.0
Follow-up (mo)	38.2 ± 21.2	38.5 ± 25.6	39.3 ± 27.2
Abnormal nerve conduction studies (*n*)	43 (81.1)	53 (81.6)	57 (60.0)
Abnormal cardiorespiratory reflexes (*n*)	43 (81.1)	55 (84.6)	62 (65.3)
ΔR6	9.4 ± 9.9	8.0 ± 9.6	12.9 ± 11.1
Valsalva ratio	1.38 ± 0.40	1.28 ± 0.37	1.40 ± 0.39

Values are means ± SD. Numbers in parentheses are percentages. ΔR6, average difference between highest heart rate during inspiration and lowest heart rate during respiration for 7 consecutive breathing cycles. Valsalva ratio, highest heart rate during Valsalva maneuver divided by the lowest rate within 30 s after maneuver.

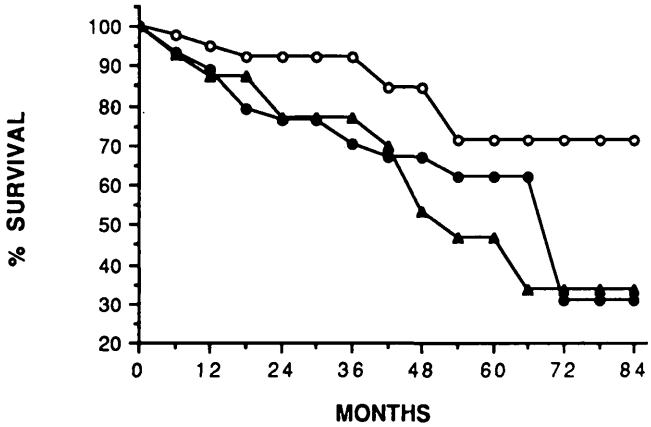

FIG. 4. Survival curves for diabetic patients with abnormalities in nerve conduction studies who had functioning pancreas transplantation (PTx; ○), failed PTx (●), or no PTx (▲).

hypothesis of a common pathogenic mechanism affecting somatic and autonomic nerve fibers. Patients with an abnormal CRR test have more marked involvement of somatic nerves shown by NCS than those with a normal CRR test (7,13). Mortality was also significantly higher among patients with abnormalities in the NCS than in those with normal results. Therefore, high mortality risk is associated with the presence of a general polyneuropathy, not exclusively with neuropathy of autonomic origin, and with other secondary complications of diabetes mellitus, i.e., vascular disease, nephropathy (17), and retinopathy (18). Consequently, the prognosis for diabetic patients should be expressed according to the severity of all these complications combined.

There is no clear evidence that improved glycemic control by exogenous insulin reverses the established symptoms and signs of autonomic neuropathy (19,20). No improvement was found in cardiovascular function tests with insulin-infusion therapies (21). Treatment with aldose reductase inhibitors was initially thought to improve certain features of autonomic nerve involvement (22), but in other studies, it has not produced significant changes (23). The presence of autonomic neuropathy has been proposed as one inclusion criterion for PTx in diabetic patients without end-stage nephropathy (24). However, a functioning pancreas graft does not result in a clear improvement in CRR test results, although it may halt progression of autonomic neuropathy to a certain degree (25,26). Our results show that patients with abnormal CRR function or NCS results improved their survival rate after receiving a functioning PTx compared with patients who underwent the same surgical procedure unsuccessfully or with patients without transplantation. Another advantage is the reported improved overall quality of life after combined pancreas-kidney transplantation than after kidney transplantation alone (27).

The relationship between an abnormal CRR and the excessive mortality in diabetic patients is not completely understood. We assume that lesions occur in different combinations in all segments of this complex reflex arc and that lesions at some sites have a greater influence on the prognosis of individual patients. An abnormal CRR is often interpreted as an indication of partial vagal denervation of the heart (28); a lesion at this site probably results in a lack of adaptation of heart function to increased demands. However, other abnormal CRR mechanisms involving chemoreceptors (29), afferents, or the brain stem may also explain mortality.

Heart disease was the most frequent cause of death (28%) in the patients studied. The frequency of myocardial infarction, more than one-third of them painless (30,31), is high in diabetic patients, nearly doubling the mortality rate (32). In addition, approximately a third of diabetic patients show evidence of depressed ventricular function in the absence of ischemia (6). Other abnormalities found among diabetic patients with autonomic dysfunction that should also be considered as possible causes of death are disorders in the reflex control of ventilation (33,34), resulting in sudden death (11), and marked postural hypotension, resulting in diminished cerebral blood flow in certain circumstances. In our patients, kidney disease was a less-frequent cause of death than in other studies (12,13). This was probably due to the high success rate of kidney transplantation in diabetic patients at our institution for over two decades (35). All of our PTx patients were nonuremic, either having their original kidneys or having received a prior or simultaneous kidney graft.

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