Cardiovascular Reflex Abnormalities in Children and Adolescents With Diabetes Mellitus

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OBJECTIVE — To assess the usefulness of specific cardiovascular reflex tests in childhood and to estimate the prevalence of cardiovascular reflex abnormalities among children with IDDM. In adults, abnormal cardiovascular reflexes are a frequent complication of diabetes, associated with increased morbidity and mortality.

RESEARCH DESIGN AND METHODS — We measured heart-rate responses to deep breathing and standing in ambulatory children with and without IDDM between 6–19 yr of age. A subgroup of the IDDM patients was retested after 1 yr.

RESULTS — We found the best techniques for detecting cardiovascular reflex abnormality in children were as follows: to record heart-rate responses to deep breathing either as the change in heart rate corrected for inspiratory heart rate or as the ratio of R-R intervals during expiration and inspiration; and to use the Maximum-minimum ratio for heart-rate responses to standing. HR-DB_c was lower in diabetic than nondiabetic children (28.6 ± 9.2% [n = 248] vs. 33.6 ± 6.8% [n = 60]; $P < 0.0005$). Similarly, E:I was lower in children with IDDM than control subjects (1.42 ± 0.19 [n = 248] vs. 1.52 ± 0.15 [n = 60]; $P < 0.0005$). In the IDDM group, 21% of the children had abnormal HR-DB_c or E:I responses. HR-STND M/m was lower in children with IDDM than control subjects (1.28 ± 0.20 [n = 167] vs. 1.38 ± 0.22 [n = 45]; $P < 0.014$). Among children with IDDM, 11.4% had abnormal HR-STND M/m responses. Overall, 29% of IDDM children tested abnormal in either HR-DB_c or HR-STND M/m; 3% were abnormal in both tests. We found no correlation of HbA_{1c} levels (n = 74) or duration of diabetes with either HR-DB, expiration to inspiration (n = 248), or HR-STND M/m (n = 167). In patients who were reevaluated after 1 yr we found a high correlation of the first and repeat HR-DB_c tests (r = 0.47, n = 75, $P < 0.0001$), E:I (r = 0.53, n = 75, $P < 0.0001$), and HR-STND M/m (r = .49, n = 37, $P < 0.002$), but no evidence of an increased number of children with cardiovascular reflex abnormality.

CONCLUSIONS — With easily performed HR-DB and HR-STND tests, we detected cardiovascular reflex abnormality in 29% of children with IDDM. We found no correlation of changes in HR-DB and HR-STND with HbA_{1c} or duration of diabetes. These tests provide an objective clinical measurement to monitor autonomic neuropathy in children with diabetes.

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CVR, CARDIOVASCULAR REFLEX; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; HR, HEART RATE; BP, BLOOD PRESSURE; sBP, SYSTOLIC BLOOD PRESSURE; dBP, DIASTOLIC BLOOD PRESSURE; HR-DB, HEART-RATE RESPONSE TO DEEP BREATHING; HR-STND, HEART-RATE RESPONSE TO STANDING; ECG, ELECTROCARDIOGRAPH; HR-DB_U, UNADJUSTED HEART-RATE RESPONSE TO DEEP BREATHING; HR-DB_C, HEART-RATE RESPONSE TO DEEP BREATHING CORRECTED FOR INSPIRATORY HEART RATE; E:I, EXPIRATORY TO INSPIRATORY RATIO; HR-STND 30:15, HEART-RATE RESPONSE TO STANDING WITH 30:15 METHOD; HR-STND M/M, HEART-RATE RESPONSE TO STANDING BY MAXIMUM/MINIMUM RATIO; R-R, TIME IN MS BETWEEN SUCCESSIVE QRS COMPLEXES; ANOVA, ANALYSIS OF VARIANCE; ANCOVA, ANALYSIS OF COVARIANCE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; CI, CONFIDENCE INTERVAL.

Damage to the autonomic nervous system is a frequent, serious complication of diabetes mellitus, which is associated with high morbidity and mortality (1–3). A high prevalence of abnormal CVR is found among adults with IDDM (4,5) and is strongly associated with clinical manifestations of autonomic neuropathy. CVR abnormalities, however, may precede overt symptomatic autonomic neuropathy by a number of years (6–8). Easily performed tests of CVR (9–12) can predict cardiac mortality, anesthetic complications (13), and development of other morbidity (14–19) in adult diabetic patients.

In light of the prognostic importance of abnormal CVRs for diabetic adults and the evidence suggesting a progression from subclinical CVR dysfunction to symptomatic autonomic neuropathy, CVR testing of asymptomatic diabetic children may be desirable. Several groups of investigators have explored the application of CVR tests to children with diabetes. Young et al. (20) reported abnormalities of HR responses to deep breathing, standing, and Valsalva maneuver in ~33% of diabetic patients 16–19 yr of age. Mitchell et al. (21,22) also found statistically significant differences of HR responses to deep breathing and standing between diabetic and nondiabetic children.

Sosenko et al. (23,24), however, found no difference in HR responses to deep breathing, standing, or Valsalva in a group of 55 diabetic subjects 8–30 yr of age, compared with control subjects. Aagenaes et al. (25) found no difference in the HR response to standing between 30 diabetic subjects 8–22 yr of age.

From these previous studies, the applicability of particular CVR test procedures and the prevalence of CVR abnormalities in young children and adolescents with diabetes is unclear. Differences in results of previous studies may be attributable to several factors: differences in methodologies, small sample sizes, and failure to adjust test results for

variations of age and sex in patients and control subjects.

Our study assesses the prevalence of abnormal CVR responses in a large population of children with IDDM. We also assessed the ease of administration and effectiveness of various CVR tests for children. We generated normative data for CVR function from a large sample of nondiabetic children.

After 1 yr, we retested a subgroup of children to evaluate the consistency of classification for the technique. We found that a pair of easily performed tests detected CVR abnormalities in 29% of asymptomatic diabetic children.

RESEARCH DESIGN AND METHODS

Selection of CVR tests

A small pilot study was conducted to evaluate the most effective battery of CVR test maneuvers for assessing prevalence of abnormalities in a large number of children. We selected 27 otherwise healthy children with IDDM, 6–19 yr of age, who were under our care and who volunteered to participate in this study. They had no reported clinical symptoms consistent with autonomic or peripheral neuropathy.

We recruited 18 nondiabetic, healthy control subjects from patients referred for evaluation of heart murmurs to the Pediatric Cardiology Clinic at the University of Maryland Hospital, and subsequently assessed as cardiologically normal (n = 18). None of these children had a history of syncope, dizziness, or arrhythmia. To expand the control group, the IDDM subjects were asked to invite a nondiabetic friend of their same sex and age to participate in the study. In this way, a similar distribution of age and sex was attained for the control group.

These children underwent testing of HR responses to deep breathing, standing, and Valsalva, as well as BP changes with standing and handgrip. Sleeping HR was evaluated with a Holter (Applied Cardiac Systems, Model 8500, Laguana Hills, CA) monitor.

The children had difficulty performing adequate handgrip and Valsalva maneuvers. They showed no difference in sleeping HR (66.6 ± 8.6 beats/min for the IDDM group vs. 65.5 ± 10.2 for the control group, $P < 0.7$) or decrease in sBP on standing (9.4 ± 6.8 mmHg for the IDDM group vs. 10.6 ± 4.9 for the control group). Therefore, only HR-DB and HR-STND were selected for further evaluation in the larger study.

Expanded study

Additional subjects were recruited from the expanded study from a summer camp for diabetic children in Glyndon, MD. Approximately 52% volunteered to participate in the study, which was open to all campers with permission from their parents. When permitted, we obtained blood samples for HbA_{1c}.

Subjects were excluded from the study for the following reasons: they were ill at the time of testing or taking medications with cardiovascular effects; they had evidence or history of chronic pulmonary or cardiac disease (1 with asthma, 2 with atrial arrhythmia, 1 with recent splenectomy); their weight was >95% for age and sex.

Reproducibility of CVR measures

To evaluate whether measures of CVR remain the same over time, we reevaluated diabetic patients who had initial CVR testing after 1 yr. Repeat testing was open to all previous participants, but we tried to reevaluate those who had initial HR-DB responses in the lower range. Signed consent for participation in these studies was obtained from parents and, when possible, the children, in accordance with a protocol approved by the University of Maryland at Baltimore Human Volunteers Research Committee .

Testing protocol

The same cardiology technician performed all tests in a relaxed environment without concomitant venipuncture or other medical care. The tests took place either in an office of the Division of Pediatric Cardiology at the University of Maryland Medical Center or in an office of the medical dispensary at Camp Glyndon. They were conducted at uniform times in the morning. Patients were asked to eat a typical breakfast and inject their usual dose of morning insulin. Tests were not performed if the subject showed hypoglycemic signs or symptoms or if the reported prebreakfast blood glucose was <70 mg%.

ECG monitoring was accomplished with a standard, single-channel recording of limb lead II or III on a Hewlett-Packard 1511B ECG recorder (Andover, MA) at 25 mm/s. The tracings were coded and read in a blinded manner by one of the authors.

HR variability with deep breathing

Before this maneuver, patients rested quietly for 5 min in the sitting position. They took six deep breaths over 1 min (six 10-s respiratory cycles). We measured the shortest R-R intervals from each of the inspiratory and the longest intervals from each of the expiratory cycles, then averaged and converted them into HR in beats/min. The difference between maximum inspiratory HR and minimum expiratory rate was calculated and expressed as HR change in beats/min, or $HR\text{-}DB_u$ (1,20). To adjust for the variability of peak inspiratory HR in children, a corrected HR-DB or $HR\text{-}DB_c$ was calculated: $HR\text{-}DB_u$ divided by the inspiratory HR and multiplied by 100. $HR\text{-}DB_c$ is expressed as a percentage. We also calculated E:I R-R intervals. Note that $HR\text{-}DB_c$ and E:I ratio are mathematically similar and differ only by a constant and use of HR versus the R-R interval measurement. In practice, when using an ECG strip, the E:I ratio is most readily calculated.

Supine and standing HR

After the subject had 5 min of supine rest, ECG was recorded and HR measured over a 6-s period. Under continu-

Table 1—*Clinical characteristics of study population*

	n	AGE (YR)	SEX (M/F)	RACIAL COMPOSITION (BLACK/WHITE)	DIABETES DURATION (YR)	WEIGHT (KG)
DIABETIC PATIENTS	248	11.6 ± 2.6	126/122	44/204	4.0 ± 3.2	42.4 ± 13.8
CONTROL SUBJECTS	60	11.9 ± 3.4	31/29	15/45	—	43.2 ± 15.3

Data are means ± SD.

ous ECG recording, the patient then rose quickly and stood quietly for 1 min. We calculated HR-STND 30:15 according to the methods of Ewing et al. (1,2). Briefly, the R-R interval of the 30th (± 1) heart beat after standing is measured and divided by the R-R interval of the 15th (± 1) heart beat. We also measured the shortest and longest R-R intervals occurring during the first minute after standing. These were similarly divided to yield the HR-STND M/m ratio (21,22). These ratios represent the subject's ability to alter HR in response to standing.

Valsalva ratio

Under constant ECG recording, patients blew into a specially adapted manometer and were instructed to maintain a constant airway pressure of 30–40 mmHg for 15 s. The maneuver was repeated three times, interrupted by 1-min rest periods. The longest R-R interval after the maneuver (indicative of the reflex bradycardia phase) is divided by the shortest R-R interval exhibited during the tachycardiac strain phase. The average of the three measurements indicates the Valsalva ratio.

Sleeping HR

After testing, subjects wore a two-channel Holter ECG recorder until the next morning, noting when they went to sleep and awoke. Recording tapes were scanned automatically and manually, using a full disclosure printout. Sleeping HR was averaged hourly. The hourly averages were used to compute the sleeping HR. These measurements were recorded only in the pilot study.

BP responsiveness

We used a Dinamap Model #1846SX Vital Signs Monitor (Critikon, FL) to eliminate technician bias and reproducibility errors in measuring BP. We performed the BP studies after the HR-response ECG studies during the pilot project. We measured sBP and dBP twice after 5 min of supine rest, immediately after standing, and every 15 s for another min. The difference between the highest sBP attained after standing and the average of the two resting sBP measurements was calculated.

Subjects squeezed a handgrip dynamometer and then were instructed to maintain 30% of their maximal effort for 3 min. In the contralateral arm, BP was measured twice at rest and every 15 s during effort. The difference between the highest dBP during effort and the averaged resting dBP was calculated.

HbA_{1c} was assayed in a commercial laboratory using a microcolumn method (26).

Statistical analysis

The influence of diabetes, age, sex, race, diabetes duration, and HbA_{1c} level was evaluated for the results of each CVR test in the expanded study with ANOVA and ANCOVA (27). The *F* statistic assessed the statistical significance of alternative models, as well as the component independent variables. Interaction terms were included in the model for diabetes with age and sex. Graphs of supine HR with respect to age and sex were generated with mean and 90% CIs derived from nondiabetic control subjects (28). Percentile ranking was derived from univariate analysis of the study samples. For individuals who underwent two studies, paired Student's *t* test and correlation analyses were used to compare results of the first and repeat tests.

Data are expressed as means ± SD. $P < 0.05$ was considered significant.

RESULTS

Comparison of CVR tests

Table 1 presents the characteristics of the entire study population. The groups of diabetic and nondiabetic children were closely matched for age, weight, sex, and race. Table 2 shows the mean values for HR-DB ($HR\text{-}DB_u$, $HR\text{-}DB_c$, E:I), HR-STND, and supine HR for the first study. We found a significant difference between children with IDDM and control subjects for all the HR maneuvers. No differences occurred in CVR test results attributable to race. Thus, further analysis of tests results evaluated the effects of age and sex. Age and sex did not affect $HR\text{-}DB_c$. In the control group the 5th percentile for $HR\text{-}DB_c$ was 22%. Age and sex did not influence E:I. In the control group the 5th percentile for E:I was 1.27. A significant interactive effect of diabetes and sex was present in $HR\text{-}DB_u$ ($P < 0.02$). Body surface area, height, and weight had no effect on any of the HR-DB measurements. Sex had a significant effect on HR-STND M/m ($P < 0.024$): Girls had lower mean responses than boys. In nondiabetic boys the mean for HR-STND M/m was 1.4 ± 0.26 with the 5th percentile of 1.04; in nondiabetic girls the mean was 1.3 ± 0.17 with the 5th percentile of 1.1.

Table 2—*CVR responses in diabetic and nondiabetic children, initial study only*

	HR-DB$_U$ (BEATS/MIN)	HR-DB$_C$ (%)	E:I	HR-STND M/M	HR-STND 30:15	SUPINE HR (BEATS/MIN)
DIABETIC PATIENTS	29.8 ± 9.3	28.6 ± 9.2	1.42 ± 0.19	1.28 ± .20	1.13 ± .18	83.2 ± 12.3
n	248	248	248	167	168	245
CONTROL SUBJECTS	34.3 ± 7.3	33.6 ± 6.8	1.52 ± 0.15	1.38 ± .22	1.24 ± .23	78.7 ± 14.3
n	60	60	60	45	47	52
P VALUE*	<0.0005	<0.0001	<0.0005	<0.014	<0.0006	<0.03

Data are means ± SD.
*Probability of difference between control and diabetic patients derived from regression sums of squares adjusted for age and sex.

Figure 1 shows the supine HR for IDDM patients and control subjects by sex. Sex strongly influenced the supine HR (girls higher than boys, $P < 0.005$), as did age (decreasing HR, $P < 0.0001$). Diabetic girls had higher HR than nondiabetic girls ($P < 0.03$).

HbA_{1c} levels were available for 74 diabetic patients with a mean of 7.0 ± 2.1% (range 3.4–13.2%). HbA_{1c} did not affect level or diabetes duration on any of the measured CVR tests for this group of children. Except for being older, the patients who permitted blood drawing for HbA_{1c} measurement did not differ in their CVR measures from those who did not permit blood drawing.

Prevalence of abnormal CVR tests

Results of HR-DB$_C$, E:I, HR-STND M/m, and supine HR were used to determine the percentage of IDDM patients with abnormal CVR. The 5th percentile for nondiabetic children was chosen as the lower limit of normal for HR-DB$_C$, E:I, and HR-STND M/m. Patients who had supine HR >95th percentile for age- and sex-matched control subjects (Fig. 1) were considered abnormal. HR-DB$_C$ and E:I identified the same patients as abnormal. Table 3 summarizes the patients classified as abnormal by these tests. In the 167 diabetic children who had both HR-DB and HR-STND M/m measured, 29% had either HR-DB$_C$ (and E:I) or HR-STND M/m <5th percentile. Of 81 diabetic girls, 15 (18.5%) had abnormally low measures of HR-STND M/m, compared with only 4 of 86 (4.7%) boys, but this difference did not attain statistical significance. Out of 167 IDDM patients, 5 (3%) (2 boys and 3 girls) had both HR-DB$_C$ and HR-STND M/m <5th percentile of control subjects.

Results of repeat CVR testing

Testing was repeated in a subgroup of IDDM patients ~1 yr after our initial encounter. Table 4 displays comparisons between the first and second sets of tests. With the exception of HR-STND 30:15, all repeat tests were significantly correlated with the first tests, and means were not different by paired Student's *t* test. Although the mean levels of both HR-DB$_C$ and HR-STND M/m were slightly lower on the repeat than the first test, these differences were not statistically significant.

Repeat testing allowed us to evaluate the consistency of classification by HR-DB. Patients with E:I <1.27 were classified as abnormal for this test, and 69% were concordantly classified on both the first and second tests (14.6% abnormal, 54.7% normal). The other 31% changed classification based on E:I from the first to second test: 13 patients (17.3%) were reclassified from abnormal to normal, and 10 patients (13.3%) went from normal to abnormal. The mean E:I (1.41 ± .14) of the 10 patients who went from normal on the first test to abnormal on the second was significantly lower than the nondiabetic control subjects ($P < 0.04$). Patients who had abnormal E:I on the first test but normal on the second also had a significantly lower mean E:I of 1.37 ± .11 on the second test than the nondiabetic control subjects ($P < 0.001$. The E:I (1.48 ± 0.18) of the 41 diabetic children (54.7%) who were consistently normal on both tests was not statistically different from the mean of the control subjects. Consistency of the classification was the same for HR-DB$_C$.

CONCLUSIONS — In this study, we found that HR-DB and HR-STND are the easiest CVR tests to perform and the most likely to detect differences between diabetic and nondiabetic children. These tests may predominantly reflect changes in parasympathetic cardiac innervation. Three other tests—HR response to Valsalva maneuver, BP response to standing, and BP response to handgrip—are more difficult to perform in children and fail to show differences between groups. These tests may predominantly reflect sympathetic cardiac innervation. The difficulty of performing adequate handgrip and Valsalva studies in children may obscure differences between diabetic and nondiabetic children. However, it also may indicate parasympathetic changes precede sympathetic alterations in childhood diabetes, as has been found in adult patients (29).

In our study the HR-DB$_C$, or E:I ratio, was not affected by age or sex and was highly correlated on repeat testing. HR-DB was not influenced by body sur-

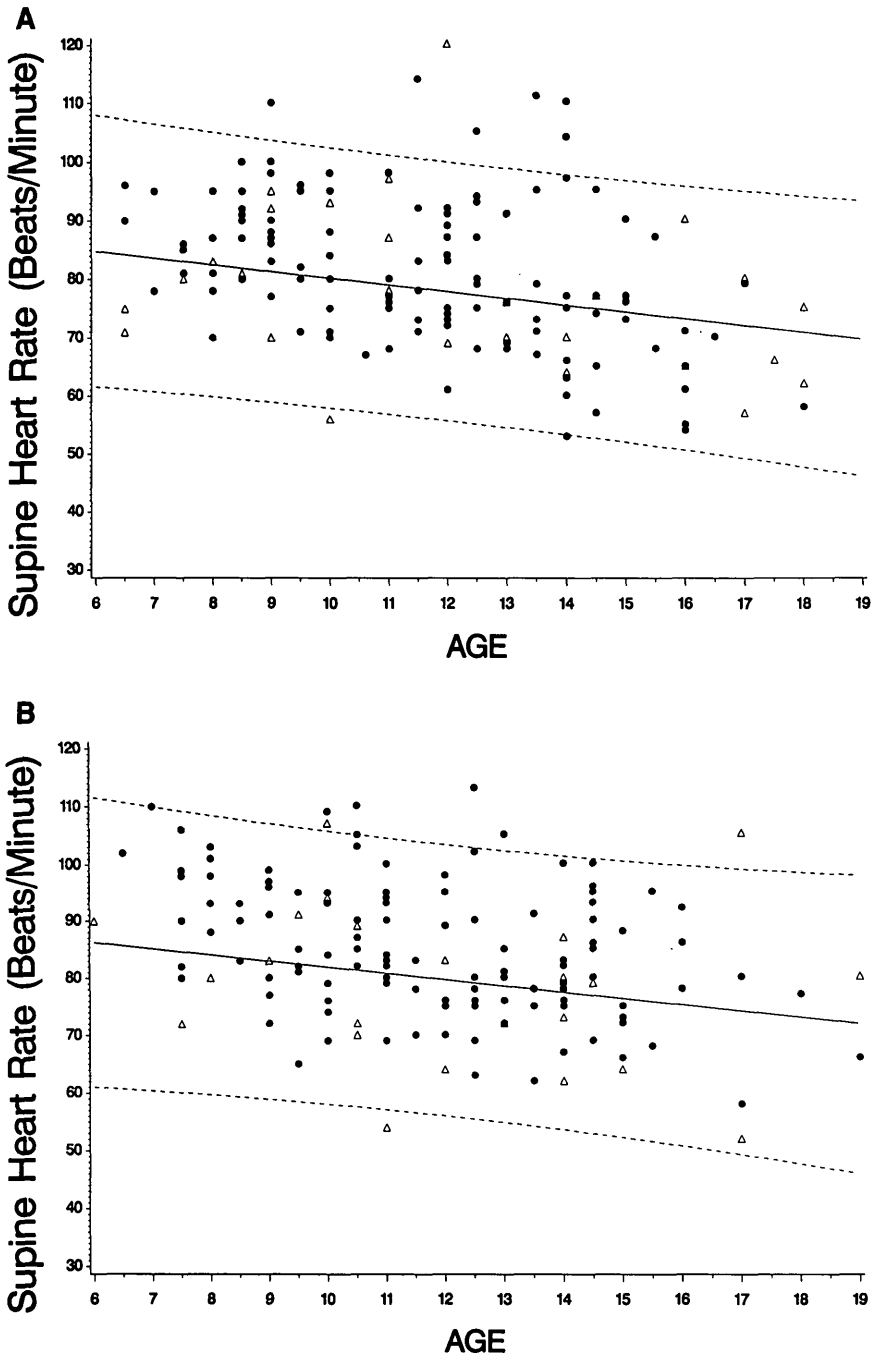

Figure 1—*Supine awake HR for male (A) and female (B) diabetic (●) and nondiabetic (△) children by age and sex. Mean and 90% CIs for nondiabetic children are shown.*

face area, height, or weight. HR-DB_c or E:I yielded the highest frequency (21%) of abnormal responses in diabetic patients.

HR-STND was significantly lower in children with IDDM than in control subjects. HR-STND M/m identified 11.4% of our IDDM group as being <5th percentile for responses developed from the nondiabetic control group. HR-STND M/m from initial testing correlated well with results of repeat testing. In contrast, HR-STND 30:15, a technique used frequently for adults, yielded results that were not correlated on repeat testing and were strongly influenced by both age and sex. For these reasons HR-STND M/m is the more desirable measurement for use in children. These observations are supported by data from Mitchell et al. (21,22).

Age and sex strongly influence the awake supine HR. The supine HR (adjusted for age and sex) was faster in diabetic than nondiabetic children. This may reflect a decline in parasympathetic outflow in diabetic patients (29). Repeat testing of supine HR after a 1-yr interval was significantly correlated with the initial results. Only 3.6% of the children with IDDM, however, had initial supine HR measurements >95% percentile for the control group. Thus, supine HR is not a sensitive indicator for CVR abnormality in individual patients. In addition, with progressive neuropathy the sympathetic outflow can be impaired and HR elevation may disappear (9), making this measurement difficult to interpret longitudinally.

We recommend the use of HR-DB_c or E:I and HR-STND M/m together for evaluation of CVR in children. Our study found that 29% of an unselected group of diabetic children responded abnormally on either one or the other of these maneuvers, and 3% were abnormal on both. Information obtained from HR-DB_c or E:I may be somewhat different from HR-STND M/m because when combined, the tests detect a larger number of abnormal responses than either test alone. These results support the findings of Mitchell et al. (21, 22) as well as Young et al. (20), who studied teenagers. In diabetic adults, concurrent abnormalities of two or more CVR tests indicates a more severe degree of cardiovascular neuropathy (29). This may have the same implication for children with diabetes.

We did not find a relationship of

Table 3—*Diabetic patients with CVR abnormality detected by first study*

	HR-DB$_c$ <5TH PERCENTILE OF CONTROL	E:I <5TH PERCENTILE OF CONTROL	HR-STND M/M <5TH PERCENTILE OF CONTROL	SUPINE HR >95 PERCENTILE OF CONTROL
ABNORMAL (*n*)	54	54	19	9
TESTED (*n*)	248	248	167	245
ABNORMAL (%)	21	21	11.4	3.6

diabetes duration or HbA_{1c} level with CVR test results in children with IDDM. This observation is in agreement with Young et al. (20), who also reported a lack of relationship between glycemic control and CVR in diabetic patients 16–19 yr of age. Sosenko et al. (23,24) described a weak correlation between HbA_{1c} and resting HR. Studies in adults have demonstrated CVR abnormalities after a short duration of diabetes in both IDDM and NIDDM patients (6,7).

The occurrence of CVR abnormalities unrelated to duration of disease or glycemic control suggests the autonomic nervous system, particularly the vagal innervation to the heart, is vulnerable in certain individuals to even a modest degree of hyperglycemia. Thus, abnormalities of CVR, particularly HR-DB, may be a very early indicator of susceptibility to complications of diabetes. A single Hb_{A1c} level available at the time of CVR testing, however, may not necessarily reflect glycemic conditions in previous months that could have contributed to the development of CVR abnormality. Further comparison of CVR tests, glycemic control, and other complications in children will help clarify this issue.

The relative frequency of abnormalities found by the various CVR maneuvers in children is similar to the experience with these tests in adult diabetic patients (29). In our study 21% of children with IDDM had abnormal HR-DB$_c$, and 11.4% had abnormal HR-STND M/m. In adults, HR-DB abnormalities also are the most prevalent form of CVR dysfunction. Ewing et al. (29) reported a prevalence of 40% for HR-DB abnormalities and 35% for subnormal HR-STND 30:15 results. Hilsted found ~40% of adult diabetic patients with HR-DB abnormalities (10), and Kennedy et al. (5) reported a 74% frequency. In general, adult patients in these studies had diabetes for a considerably longer duration and had other clinical manifestations of diabetic complications compared with the diabetic children in our study. The higher reported prevalence of CVR in adults compared with the data from children suggests that neuropathic changes underlying CVR abnormalities may progress or develop after long duration of diabetes.

Our study showed no increase in the number of children classified as abnormal by HR-DB or HR-STND M/m after 1 yr. We found 69% were consistently classified as abnormal or normal on repeat CVR testing by HR-DB$_c$ or E:I, and 31% were reclassified on repeat testing. The children who changed classification from normal on the first test to abnormal on the second had average E:I ratios significantly lower than control subjects on initial testing (1.41 ± 0.14 vs. 1.52 ± 0.15, $P < 0.04$). Patients classified as abnormal on the first test, but who reached or exceeded the 5th percentile on the second test, also had a lower E:I than control subjects (1.37 ± 0.11 vs. 1.52 ± 0.15, $P < 0.001$). Thus, patients who changed classifications also exhibited a degree of CVR impairment that differentiated them from the control group. Further observation and testing is needed to evaluate the clinical and biological significance of these findings.

Of 237 adult patients studied by Ewing et al. (29), who had repeat CVR studies, 20% worsened, 74% were unchanged, and 6% improved over the period of observation. In a group of diabetic patients 16–19 yr of age, the prevalence of HR-DB abnormalities increased from 19–28% after 2.5 yr (30). In these young adults HR-DB responses were inversely correlated to albuminuria, and their increased frequency of diabetic complications was associated with poor

Table 4—*Correlation between first and second CVR studies in a subgroup of diabetic children*

	HR-DB$_u$ (BEATS/MIN)	HR-DB$_c$ (%)	E:I	HR-STND M/M	HR-STND 30:15	SUPINE HR (BEATS/MIN)	AGE (YR)
n	75	75	75	37	40	71	75
CVR STUDY							
FIRST	27.3 ± 9.1	26.3 ± 9.1	1.38 ± .18	1.24 ± .17	1.13 ± .15	84.3 ± 11.0	11.0 ± 2.3
SECOND	26.5 ± 8.9	26.0 ± 9.7	1.37 ± .20	1.20 ± .15	1.20 ± .19	83.1 ± 15.4	12.0 ± 2.3
r	0.41	0.47	0.53	0.49	0.15	0.46	
P	<0.0002	<0.0001	<0.0001	<0.002	<0.36	<0.0001	

Data are means ± SD.

glycemic control. Therefore, young children who demonstrate CVR abnormalities might be expected to develop more extensive abnormalities over time, particularly if glycemic control is poor.

Euglycemia may prevent the progression of abnormal CVR tests. Jakobsen et al. (31) showed that HR-DB and HR-STND were unchanged over a 2-yr period when good control was established by continuous subcutaneous insulin infusion, whereas patients on conventional therapy showed worsening of CVR function. After pancreas transplantation, no change in HR-DB was observed (32,33), and improvement in response to Valsalva was noted (33). Thus, progression of CVR dysfunction may be preventable with excellent glycemic control.

Autonomic neuropathy in diabetic adults has been associated with sudden cardiac death, renal failure, anesthesia complications, and increased risk of mortality (1–3,14–19). With prolonged duration of diabetes, development of other complications, such as hypertension, atherosclerosis, dyslipidemia, and nephropathy, contribute to the already increased risk associated with autonomic neuropathy (29,30,34). A diabetic child with persistent CVR abnormalities therefore may face an increased burden of cardiovascular risk.

On the basis of our findings, we recommend measurement of HR- DB_c and HR-STND M/m in children with diabetes. These tests are easy to perform even in relatively young children. This methodology will facilitate further study of the relationship of CVR abnormalities with the development of other complications in childhood diabetes. In children who demonstrate CVR abnormality in response to HR-DB and/or HR-STND tests, extra effort should be made to evaluate sympathetic CVR, including measurement of BP changes with standing, and, if feasible, responses to Valsalva maneuver and handgrip. Other clinical manifestations of neuropathy should be sought as well. Until further information is available, we recommend that a child with persistently abnormal CVR responses be managed similarly to children who develop other early metabolic complications of diabetes. Particular consideration should be given to possible risks of anesthesia and other procedures for children with documented CVR abnormalities (13).

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