# Beat-to-Beat Blood Pressure Response in Asymptomatic IDDM Subjects

Iris B. Goldstein, PhD
Bruce D. Naliboff, PhD
David Shapiro, PhD
Harrison J.L. Frank, MD, PhD

**Nine insulin-dependent diabetic (IDDM) patients (aged 25–37 yr) with no symptoms of autonomic neuropathy and 15 healthy control subjects (aged 26–39 yr) were studied at rest and during tests of Valsalva maneuver, deep breathing, cold pressor, and postural change from sitting to standing. Continuous (beat-to-beat) measures were taken of heart rate, systolic blood pressure, diastolic blood pressure, and skin conductance. The diabetic patients were differentiated from the control group by the following: less variability in diastolic blood pressure during deep breathing, failure to exhibit diastolic blood pressure decreases during recovery from a cold pressor stimulus, a flatter blood pressure response pattern when changing from sitting to standing, and a smaller standing ratio (maximum/minimum) for R-R interval. Among the patients, age was negatively correlated with systolic and diastolic standing ratios and diastolic blood pressure variability during deep breathing. By use of the tracking cuff, a method of continuously recording blood pressure noninvasively, we have been able to assess subtle blood pressure changes, thereby revealing signs of sympathetic dysfunction in a group of relatively young diabetic patients with no symptoms of neuropathy. The tracking-cuff method of recording blood pressure has potential in further research on autonomic functioning in diabetic patients. *Diabetes Care* 11:774–79, 1988**

By means of a series of simple, noninvasive tests, investigators have studied diabetic patients and have found that autonomic involvement is much more prevalent than was once thought, even in the absence of overt symptoms (1–5). Loss of normal heart-rate variation is one of the most sensitive indicators of parasympathetic damage to autonomic pathways and is generally evident in autonomic function tests such as deep breathing, the Valsalva maneuver, and postural change (4,6–9). Other tests, such as the blood pressure response to standing and to isometric handgrip, are used to evaluate sympathetic pathways. Abnormal responses to these tests are associated with more severe autonomic neuropathy and have generally been demonstrated when some parasympathetic impairment already exists (1,5,10). However, it is possible that the parasympathetic dysfunction is detected before sympathetic change in newly diagnosed diabetic patients due to the fact that tests of heart-rate response that assess beat-to-beat fluctuations are able to pick up more subtle changes than tests of the blood pressure response that monitor blood pressure no more than once or twice per minute (11,12).

Using a blood pressure tracking system developed in our laboratory and validated against intra-arterial recordings (13), we are able to record blood pressure noninvasively on a beat-to-beat basis. The purpose of this study was to determine if the use of continuous measures of blood pressure and heart rate during tests of autonomic function can discriminate cardiovascular differences between young patients with insulin-dependent diabetes mellitus (IDDM) and a group of healthy matched controls.

## MATERIALS AND METHODS

**Subjects.** Nine IDDM patients were recruited (after obtaining informed consent) from the outpatient diabetes clinic of the University of California, Los Angeles. Pa-

From the Departments of Psychiatry and Biobehavioral Sciences and of Anesthesiology, University of California, Los Angeles; Behavioral Medicine Research, Sepulveda V.A. Medical Center, Sepulveda; and the Department of Medicine, Long Beach V.A. Medical Center/University of California, Irvine, California.
Address correspondence and reprint requests to Dr. David Shapiro, Department of Psychiatry, UCLA, 760 Westwood Plaza, Los Angeles, CA 90024-1759.

**TABLE 1**
**Characteristics of control and diabetic subjects**

| | Control subjects | Diabetic subjects |
|---|---|---|
| Sex (F/M) | 9/6 | 5/4 |
| Age (yr) | 30.9 ± 4.2 (26–39) | 32.1 ± 4.2 (25–37) |
| Duration of illness (yr) | | 20.1 ± 5.5 (11–30) |
| Random glucose (mg/dl) | 95.4 ± 11.5 (80–125) | 196.4 ± 84.2 (73–319) |
| $HbA_{1c}$ (%) | 5.2 ± 0.5 (4.5–6.1) | 10.3 ± 2.2 (7.5–14.4) |
| Creatinine (mg/dl) | | 0.9 ± 0.2 (0.7–1.2) |

Values are means ± SD with ranges in parentheses.

tients on antihypertensive drugs and other medications that alter cardiovascular responses were excluded, as were those with chronic renal failure, a history of recent myocardial infarction, or clinically significant arrhythmias. Patients had complete medical examinations at the diabetes clinic. Complications were defined in terms of small-vessel damage, including retinopathy (by eye exam), nephropathy (proteinuria >30 mg/dl on a random urine and serum creatinine >1.3 mg/dl), and peripheral neuropathy (assessed clinically by measuring vibration sensation and ankle reflex). Subjective symptoms of autonomic neuropathy such as orthostatic blood pressure, gastroparesis, and sexual dysfunction were assessed during a physician's interview. All of the patients had diabetes for at least 11 yr with no symptoms of neuropathy or nephropathy. A urine dipstick showed that protein in the urine was <30 mg/dl for all patients. Four of the patients had signs of retinopathy (3 background, 1 proliferative).

The control group consisted of 15 healthy volunteers solicited through the campus newspaper. Both groups were made up of students and university employees of similar age. All of the subjects were seen ~1 h after either breakfast or lunch. They were asked to abstain from coffee and cigarettes on the day of their laboratory measurements. Characteristics of the control and diabetic subjects can be found in Table 1.

**Physiological recording methods.** A digital computer controlled all aspects of the experiment, including data processing, storage, and operation of the tracking-cuff system. Physiological signals were processed through a Beckman type R polygraph.

Heart rate (ECG) was monitored by means of a voltage level device that detected the R-wave in each cardiac cycle. Heart period (R-R interval) was timed to the nearest millisecond.

Blood pressure was measured with a continuous beat-to-beat tracking-cuff system developed in our laboratory. It has been validated against intra-arterial recordings (13) and has been used in several studies, including those involving postural change (14–16). A miniature piezoelectric microphone was taped to the skin ~5 cm above the elbow over the brachial artery of each arm. A cuff was placed over the microphone on the right arm to record systolic blood pressure and on the left arm to record diastolic blood pressure. A polygraph tracing il-

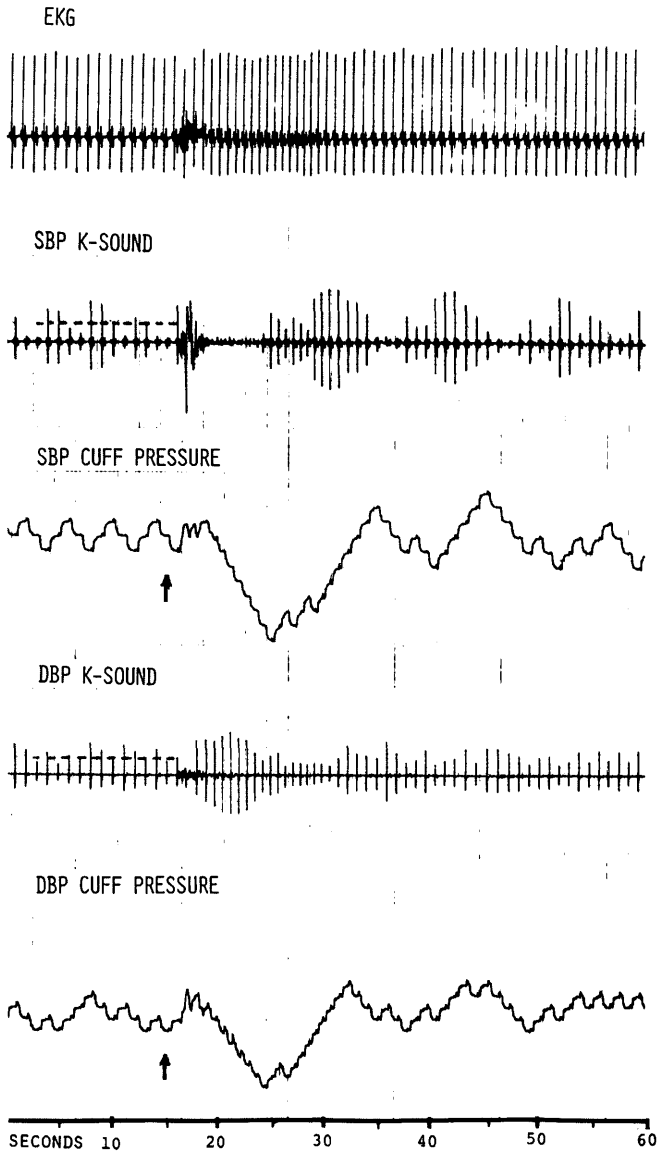


**FIG. 1. Polygraph record shows operation of blood pressure tracking system during postural change trial in control subject. Pressure in each cuff was increased or decreased by 3 mmHg after each R-wave in ECG, depending on presence or absence of criterion Korotkoff (K-) sound. Systolic blood pressure (SBP) cuff pressure was increased by 3 mmHg with each presence of criterion SBP K-sound and decreased by 3 mmHg for each absence of K-sound. *Broken line* indicates SBP K-sound detection level, which was determined clinically by stethoscope. Same procedure was used to measure diastolic blood pressure (DBP), except that cuff pressure was decreased with each presence and increased with each absence of criterion DBP K-sound. Resulting SBP and DBP cuff pressures are used as estimates of beat-to-beat SBP and DBP, respectively. Blood pressure level just before standing up (*arrow*) was 120/70 mmHg, and initial trough after standing was 99/55 mmHg.**

lustrating the operation of the tracking cuff during the change from sitting to standing is shown in Fig. 1.

Respiration rate was measured by means of a strain gauge belt placed around the lower rib cage to verify that 6 breaths/min were obtained during the deep breathing. Respiration rate was not analyzed as a dependent variable.

**Procedures.** Subjects were seated in a comfortable lounge chair, and blood was drawn for glucose determination by means of a Beckman glucose analyzer and for $HbA_{1c}$ determination by a boronate affinity column kit (Endocrine Sciences, Tarzana, CA). Normal values for nondiabetic controls (determined in our laboratory) ranged from 4.0 to 6.8% with a mean and SD of 5.1 ± 0.7%. For the next 20 min, subjects sat quietly during the hookup of the various devices. All data were collected during 60-s trials with 30 s intervening between trials. This timing was based on 60-s cuff inflations, followed by a 30-s deflation period to allow for recirculation of blood and to avoid discomfort. The session began with two baseline trials followed by a series of tests presented in a counterbalanced order, with 5 min of rest intervening between each task. The tasks were as follows.

*1*) Valsalva maneuver: using the procedure of Ewing et al. (17), two trials were run with a minimum of 3 min between trials. A Valsalva ratio was calculated for the maximum R-R interval after the maneuver (26–50 s) to the minimum R-R interval (16–40 s), which usually came either during the maneuver or shortly thereafter. Blood pressure ratios were calculated by dividing the maximum blood pressure during the maneuver or shortly thereafter (systolic blood pressure, 10–25 s; diastolic blood pressure, 12–40 s) by the minimum blood pressure toward the end of the maneuver or after its completion (systolic blood pressure, 20–40 s; diastolic blood pressure, 30–50 s). The periods for which ratios were obtained vary for the three measures because of the differing patterns of response, with maximum and minimum points occurring at different times (18).

*2*) Deep breathing: there were two trials of deep breathing at 6 breaths/min (19) paced by a metronome. Differences between the maximum and minimum values for each trial were obtained for R-R interval, systolic blood pressure, and diastolic blood pressure.

*3*) Cold pressor: subjects placed their right hand into a bucket of ice water (4°C) for one 60-s trial and sat quietly with the hand removed from the ice water during a second 60-s trial.

*4*) Postural change: the sequence began with five trials with subjects seated with arms extended downward in a straight-backed chair for trial 1 (sit). Fifteen seconds into trial 2 (sit/stand) subjects stood up (Fig. 1), remained standing for trials 3 and 4 (stand), and sat down again 15 s after the start of trial 5 (stand/sit). Because of its relevance to orthostatic stress, only the sit/stand trial is discussed. For each individual sit/stand trial, we calculated a standing ratio (8) similar to 30:15 (17) as follows: the maximum R-R interval (10–35 s after standing up) divided by the minimum R-R interval (1–25 s after standing up). Comparable indices were obtained for systolic blood pressure and diastolic blood pressure with the ratio of the largest to the smallest blood pressure during these periods. Note that the ratios were based on a change to standing from a prior seated position, rather than the supine state used in most of the diabetes literature. The results of our previous studies indicate that the pattern and timing of heart-rate changes from sitting to standing do not show any major differences from the typical supine-to-standing response curve (14,15,20). Peaks and troughs were also determined for each subject during the sit/stand trial.

## RESULTS

Except for the test of postural change, data were analyzed by a series of two-way analyses of variance (ANOVA) in a group (2) × trial (2) design. Where appropriate, post hoc analysis for testing simple effects was

**TABLE 2**
**Results of cardiovascular autonomic function tests for control and diabetic subjects**

| Test | Heart rate (beats/min) | | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | |
|---|---|---|---|---|---|---|
| | Control | Diabetic | Control | Diabetic | Control | Diabetic |
| Baseline (1-min mean) | 74.0 ± 9.0 | 79.6 ± 14.0 | 116.0 ± 8.8 | 117.4 ± 8.8 | 75.3 ± 7.2 | 77.4 ± 6.0 |
| Valsalva maneuver (maximum:minimum) | 1.76 ± 0.38* | 1.51 ± 0.32* | 1.26 ± 0.08 | 1.23 ± 0.07 | 1.42 ± 0.13 | 1.40 ± 0.19* |
| Deep breathing (maximum − minimum) | 23.2 ± 8.6 | 18.7 ± 10.2 | 22.2 ± 5.3 | 20.1 ± 3.7 | 19.4 ± 3.1† | 16.9 ± 3.4 |
| Cold pressor | | | | | | |
| Stimulus trial (1-min mean) | 74.7 ± 7.7 | 79.8 ± 15.0 | 121.5 ± 11.8 | 129.2 ± 11.7 | 82.2 ± 8.0 | 84.8 ± 7.4 |
| Recovery trial (1-min mean) | 69.5 ± 7.2 | 76.2 ± 17.3 | 121.1 ± 15.4 | 125.6 ± 9.8 | 78.6 ± 7.2‡ | 83.5 ± 6.2 |
| Postural change (maximum:minimum) | 1.47 ± 0.19*† | 1.28 ± 0.22* | 1.27 ± 0.07 | 1.23 ± 0.10 | 1.49 ± 0.13 | 1.39 ± 0.19 |

Values are means ± SD for control ($n$ = 15) and diabetic subjects ($n$ = 9).
*Measured as R-R interval.
†$P < .05$ vs. diabetic subjects.
‡$P < .05$ vs. diabetic subjects for change from stimulus to recovery trial.

**TABLE 3**
**Heart-rate and blood pressure responses of control and diabetic subjects at 3 phases of sit/stand trial**

| | Heart rate (beats/min) | | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | |
|---|---|---|---|---|---|---|
| | Control | Diabetic | Control | Diabetic | Control | Diabetic |
| Sit | 73.0 ± 7.7 | 77.9 ± 17.1 | 123.0 ± 12.9 | 127.7 ± 11.6 | 72.4 ± 8.3 | 78.0 ± 7.3 |
| Trough/peak | 96.2 ± 8.2 | 95.7 ± 11.5 | 102.8 ± 15.6* | 112.2 ± 18.2 | 53.5 ± 9.0 | 61.3 ± 10.1 |
| Stand | 80.7 ± 8.4 | 84.8 ± 16.1 | 121.2 ± 16.5 | 120.9 ± 17.6 | 71.2 ± 8.2 | 74.7 ± 8.8 |

Values are means ± SD for control ($n$ = 15) and diabetic ($n$ = 9) subjects. See text for definition of *phase*.
*$P < .05$ vs. diabetic subjects.

performed with use of the Newman-Keuls test (21). Most of the results of the various tests are summarized in Table 2. Where there were no significant differences between the two trials, the mean of these trials is presented in Table 2.

**Baseline.** There were no significant differences between the control and diabetic groups during the baseline procedure.

**Valsalva maneuver.** Characteristic patterns for heart rate and blood pressure were exhibited during the Valsalva maneuver (7,11,22), but analyses of the Valsalva ratio revealed no group differences for any of the variables.

**Deep breathing.** The controls had a significantly larger diastolic blood pressure difference score (maximum − minimum) (19.4 ± 3.1 mmHg) compared with the diabetic subjects (16.9 ± 3.4 mmHg) during deep breathing [$F(1/22) = 5.41$, $P < .03$].

**Cold pressor.** Both groups responded similarly to the cold pressor stimulus. However, a significant interaction of group × trial [$F(1/22) = 4.8$, $P < .04$] for diastolic blood pressure was due to the fact that the controls exhibited a significant drop of 3.6 mmHg from the stimulus trial to the recovery trial, whereas the diastolic blood pressure of the diabetic group showed almost no change during the minute after removal of the hand from the ice water ($P < .05$).

**Postural change.** The diabetic group had a standing ratio of 1.28 for R-R interval, and the control group had a ratio of 1.47 ($t = 5.14$, $P < .03$). The systolic and diastolic standing ratios for postural change did not differ significantly between groups.

To analyze the sit/stand trial in terms of phases, blood pressures were converted into second-to-second values (23). This does not change the patterning of the data but puts it on a time basis so that there is comparability from subject to subject. For each subject the sit/stand trial was divided into three different phases: sitting (mean of 6–15 s), peak or trough (16–35 s), and standing recovery (47–56 s). Systolic blood pressure did not fall to as low a level for the diabetic subjects (112.2 ± 18.2 mmHg) as it did for the controls (102.8 ± 15.6 mmHg) during phase 2 (trough) (Table 3). This was confirmed by the significant interaction [$F(2/44) = 4.16$, $P < .02$] of group × phase in an ANOVA comparing the three phases for the two groups and the subsequent Newman-Keuls analysis ($P < .05$). A similar trend was exhibited for diastolic blood pressure [$F(2/44) = 2.6$, $P < .08$] (Table 3). These effects reflect not only the somewhat higher blood pressure levels of the diabetic group, but also the tendency for the response to orthostatic stress to be somewhat flattened. Heart-rate effects were not different between the two groups.

**Correlations.** With increasing age, systolic standing ratio ($r = -.80$, $P < .01$), diastolic standing ratio ($r = -.84$, $P < .01$), and diastolic blood pressure variability during deep breathing ($r = -.76$, $P < .02$) were found to decrease in the diabetic group. There were no significant correlations with age in the control group. Metabolic control and duration of diabetes were not significantly correlated with any of the physiological measures.

## DISCUSSION

The results of this study demonstrate that young diabetic subjects with a long duration of illness and without autonomic neuropathy (not detectable under normal resting conditions) can be differentiated from a group of nondiabetic controls in their blood pressure responses to a series of relatively simple tasks with the aid of the blood pressure tracking cuff. Although the tracking cuff has not been utilized with a population of diabetic patients, its validation against intra-arterial recordings makes it a useful tool (13). A limitation of this system with rapidly changing tests, such as postural change and the Valsalva maneuver, is that the responses may appear to be delayed by a few seconds, although the pattern of responding obtained in this manner appears to be similar to the data obtained in intra-arterial recordings (18,20,22,24,25).

We found that the diabetic subjects had less variability in diastolic blood pressure during deep breathing and less recovery to baseline of diastolic blood pressure during a period 30–90 s after a cold pressor stimulus. In addition, the diabetic group had a flatter systolic response pattern (with a similar tendency for diastolic blood pressure) when changing position from sitting to standing. The only heart-rate difference between groups was a smaller standing ratio for R-R interval in the diabetic group.

On measures of heart rate during deep breathing and the Valsalva task, the diabetic and control subjects re-

sponded similarly. This is in contrast with the concept that reduced heart-rate variability during breathing is one of the most sensitive signs of autonomic dysfunction, often preceding the appearance of autonomic symptoms by several years (1,6,7,26,27). Indications of abnormalities in the postural response, however, are more likely to be found in diabetic individuals who already display autonomic symptoms (8).

The smaller standing heart-rate ratio for the diabetic group compared with control group could be, according to Ewing et al. (28), the beginning of signs of vagal damage. In contrast, however, others stress the influence of both parasympathetic and sympathetic nerves in postural change, claiming that the initial heart-rate increase is due to parasympathetic withdrawal, whereas the subsequent maximum heart-rate increase is probably mediated by the sympathetic nervous system (29,30). The rebound bradycardia, on the other hand, is caused by increased parasympathetic tone.

The aberrant blood pressure pattern of the diabetic subjects during the trough of the sit/stand trial represents an overall decreased responsiveness. Although not indicative of orthostatic hypotension, this pattern of responding may be the beginning of changes in sympathetic vasoconstrictor activity affecting peripheral vascular resistance (31). Note that among the diabetic patients there were significant differences in the standing blood pressure ratios between individuals with and without signs of retinopathy, those patients with retinopathy having the lower ratios. No such differences were present for the heart-rate ratio. In addition, the patients with retinopathy were not distinguished from the other diabetic patients on any of the other tests. These results are in accordance with the findings of Sundkvist et al. (32) of a delayed diastolic blood pressure rise in response to upright tilt among diabetic patients with retinopathy. The fact that the diastolic abnormality could sometimes be found in the absence of vagal damage supports our findings that sympathetic damage may occur before any parasympathetic defect. Similar signs of sympathetic dysfunction in the diabetic subjects may be indicated by their differing diastolic blood pressure reactions during recovery from cold pressor and during the deep breathing task. The cold pressor response is quite complex and is believed to measure the integrity of sympathetic efferent fibers or of efferent vascular receptors (33). With increasing age these blood pressure responses were more aberrant. This finding should be followed up with an investigation of a larger sample of subjects having a broader age range.

In conclusion, it must be emphasized that our results are at variance with the commonly held view that signs of parasympathetic dysfunction appear earlier in diabetic individuals than signs of sympathetic dysfunction (5,12). The question of whether sympathetic or parasympathetic nerve damage occurs first is rather complex, with differing viewpoints in the literature (11,31,34). It is likely that the findings in this study are due primarily to the fact that our blood pressure measurements are able to assess more subtle change than those of investigators who have been unable to find such differences in asymptomatic diabetic patients. Ewing and Clarke (12) suggest that studies of diabetic patients have generally been conducted with heart-rate tests that are much more sensitive than those of blood pressure functions. The ability to track blood pressure noninvasively on a beat-to-beat basis provides one with an additional tool to examine autonomic neuropathy in diabetes and may also be useful in developing behavioral interventions for the management of orthostatic hypotension (15,35).

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