

Deep Breath Test for Evaluation of Autonomic Nervous System Dysfunction in Familial Dysautonomia

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ABSTRACT: **Background:** Familial dysautonomia is a genetic disease that affects the sensory and autonomic nervous systems with varying severity. The deep breath test is one of several measures used to assess the severity of autonomic diseases, but its value in familial dysautonomia has not yet been investigated.

Objectives: To determine the diagnostic value of the DBT in patients with familial dysautonomia.

Methods: Eight patients with familial dysautonomia and eight healthy volunteers were examined by electrocardiography for 1 minute at rest and during forced deep breathing. The following values were recorded: maximum expiratory and minimum inspiratory heart rate and the difference between them ($\Delta E/I$), standard deviation of the heart rate values, interbeat intervals, and E/I ratio. Spectral power analysis of heart rate variability was also performed.

Results: The patients with familial dysautonomia showed a lesser change in heart rate in response to the change in breathing pattern than the controls. Mean values in the study group were significantly higher for minimal inspiratory heart rate and significantly lower for $\Delta E/I$, heart rate standard deviation and E/I ratio, indicating a non-flexible heart response and abnormal parasympathetic function. These findings were supported by power spectral analysis.

Conclusions: Patients with familial dysautonomia have a significantly disturbed response to physiological stimuli. The DBT may serve as a reliable means to quantify autonomic dysfunction in this patient population.

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KEY WORDS: familial dysautonomia, deep breath test, autonomic nervous system, heart rate variability, spectral power analysis

Familial dysautonomia, first described by Riley and Day in 1949 [1], is an autosomal recessive disorder characterized by abnormal development of the sensory and autonomic nervous systems as well as progressive neuronal degeneration

DBT = deep breathing test
E/I = expiratory/inspiratory

[2,3]. It is also termed hereditary sensory and autonomic neuropathy type 3 [2]. A mutation in the *IKBKAP* gene located in the long arm of chromosome 9 is responsible for 99% of cases [2]. The disease occurs almost exclusively in Ashkenazi Jews (i.e., of East European descent), with a worldwide incidence of 1:10,000 to 1:20,000 [2,4].

The sympathetic system dysfunction in FD is usually pronounced, and both the sympathetic ganglia and the intermediolateral spinal columns are grossly affected [5]. The parasympathetic dysfunction varies in severity [6]. The clinical presentation includes alacrimation, frequent changes in skin color, body temperature dysregulation, dysphagia, gastrointestinal dysmotility, recurrent aspiration pneumonia, spinal deformity, and tendency to injury [3]. Cardiovascular dysregulation is common and is characterized by a lack of compensatory increases in heart rate in response to orthostatism [5] and labile blood pressure [4]. Studies also report insensitivity to hypercapnia and hypoxia [3]. Non-invasive tests currently used to evaluate the autonomic dysfunction in FD include infra red pupillometry to measure the light-reflex response as a sign of sympathetic and parasympathetic nerve dysfunction [7], and the cold face test to evaluate the parasympathetic response to modified diving reflex stimuli [8].

It is well recognized that a change in breathing pattern can alter the autonomic regulation of the cardiovascular system [9]. The aim of the present study was to determine the diagnostic value of the deep breath test in patients with FD. Our search of the literature yielded no data on this issue.

PATIENTS AND METHODS

A prospective case series design was used. The research protocol was approved by the Institutional Helsinki Committee. All participants provided written informed consent.

The study group included 10 patients with FD, 6 males and 4 females. These patients account for about 8% of all known patients with FD currently living in Israel. The average age at diagnosis was 2 years. The control group consisted of eight age-

FD = familial dysautonomia

and gender-matched healthy volunteers. None of the patients (in both groups) were smokers and all were diabetes-free.

All participants were asked to avoid smoking as well as intake of caffeinated beverages or other stimulants for 12 hours prior to the DBT, and to avoid strenuous exercise for 24 hours prior to the test. In all cases, the test was conducted between 4:00 and 6:00 p.m. to avoid the circadian influence on heart rate and autonomic nervous system function. Room temperature was maintained at 21–23°C. To prevent sympathetic overactivity, subjects were requested to empty their bladder before the test.

Before the test began, participants were asked to lie motionless for 20 minutes in a quiet room without external interference for measurement of baseline heart rate (60 sec). Thereafter, a electrocardiographic examination lasting 1 minute was conducted with the MAC 5000 device (Marquette, GE Healthcare, Milwaukee, WI, USA), during which subjects were asked to remain in the prone position and to perform forced breathing six times. The deep breathing test was repeated and the results were averaged. The ECG readings were transmitted to a computer, and the heart rate values

were extracted on the basis of the intervals between the R spikes. Maximal heart rate during expirium and minimal HR during inspirium was measured, and the difference between the two was calculated ($\Delta E/I = \text{MaxHR} - \text{MinHR}$). The standard deviation of the heart rate values and of the interbeat intervals was computed. The E/I ratio was calculated by dividing the longest mean RR interval during expirium by the shortest RR interval during inspirium [10].

Spectral analysis of heart rate variability was performed with a Matlab-based computer code kindly provided by the Department of Applied Physics, University of Kuopio, Finland. Spectral density was calculated using the non-parametric fast Fourier transform algorithm for low (0.04–0.15 Hz) and high (0.15–0.5 Hz) frequency bands. Low frequency changes are mediated by both sympathetic and parasympathetic activity at rest; high frequency changes are linked to the respiratory influence on heart rate and reflect parasympathetic activity [11–14]. Both LF and HF measurements were recorded in normalized units [14].

The LF/HF ratio was calculated as an indicator of the sympathetic-parasympathetic balance [15,16]. The square root of the mean squared difference of successive RR intervals was calculated as an indicator of the short-term component of rate variability [14,15].

Results are presented as means and standard deviations. Findings were compared between the groups by Student's *t*-test. A *P* value of 0.05 was considered statistically significant.

Table 1. Heart rate changes and frequency domain parameter in patients with familial dysautonomia and healthy controls

Parameter	Control	FD	Pvalue
Age (yrs)	24.37 ± 9.56	25.5 ± 12.5	NS
Maximal expiratory HR (beats/min)	88.87 ± 14.98	96.25 ± 13.34	NS
Minimal inspiratory HR (beats/min)	50.5 ± 4.69	73.37 ± 8.26	< 0.001
$\Delta E/I$	38.37 ± 15.38	22.87 ± 13.15	0.048
HR-SD	0.137 ± 0.038	0.049 ± 0.020	< 0.001
E/I ratio	1.77 ± 0.34	1.32 ± 0.2	<0.01
RR-SD baseline (sec)	0.07 ± 0.05	0.03 ± 0.01	0.05
RR-SD DBT (sec)	0.13 ± 0.04 (< 0.01)	0.04 ± 0.02 (NS)	< 0.001
RMSSD baseline (msec)	85.36 ± 67.05	28.55 ± 12.89	0.032
RMSSD DBT (msec)	115.69 ± 45.96 (NS)	24.54 ± 15.18 (NS)	< 0.001
LF baseline (nu)	27.79 ± 13.81	37.1 ± 17.86	NS
LF DBT (nu)	72.39 ± 8.89 (< 0.001)	66.16 ± 13.55 (< 0.01)	NS
HF baseline (nu)	72.21 ± 13.81	62.9 ± 17.86	NS
HF DBT (nu)	27.61 ± 8.89 (< 0.001)	33.96 ± 13.58 (< 0.01)	NS
LF/HF baseline	0.44 ± 0.35	0.73 ± 0.57	NS
LF/HF DBT	3.02 ± 1.46 (0.001)	2.93 ± 2.92 (NS)	NS

HR = heart rate, $\Delta E/I$ = (maximal HR)-(minimal HR), HR-SD = standard deviation of HR during 1 minute DBT, SD-RR = standard deviation of interbeat interval, RMSSD = mean squared root of the difference of successive RR intervals, DBT = deep breath test, HF = high frequency, LF = low frequency. NS = not significant.

Note: The *P* value given in parenthesis refers to the change in examined parameters after the DBT from baseline.

The *P* value column refers to the difference in examined parameters between the FD and control groups.

RESULTS

Two patients with FD found it difficult to coordinate their breathing pace to create a maximum expiratory and inspiratory force, and their findings were excluded from the final analysis. The results of the control group and the eight remaining patients are shown in Table 1. The DBT results in a 31 year old healthy female volunteer and 33 year old female with FD are given in Figures 1 and 2 respectively. There was no significant difference between the control and FD groups in mean MaxHR during expirium. The control group had a significantly lower mean minimal inspiratory HR compared to the FD group ($P < 0.001$) and a significantly higher mean $\Delta E/I$ ($P = 0.048$), higher HR-SD ($P < 0.001$) and higher E/I ratio ($P < 0.01$).

The study group had a significantly lower RR-SD than the control group, both during rest and after DBT stimulation, indicating a lesser heart rate variability. Moreover, RR-SD was not significantly altered by DBT, as was observed in the

MaxHR = maximum heart rate

MinHR = minimum heart rate

RR = interbeat

LF = low frequency

HF = high frequency

HR-SD = standard deviation of heart rate values

RR-SD = standard deviation of interbeat intervals

Figure 1. Deep breath test results in a 31 year old healthy female volunteer

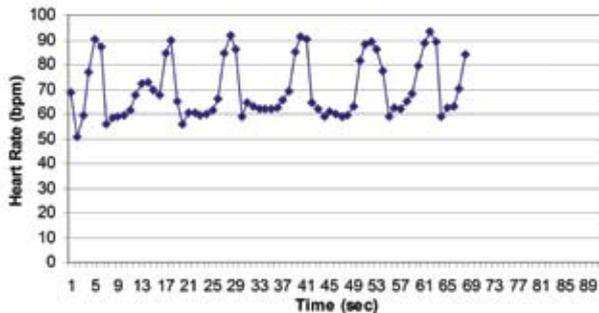
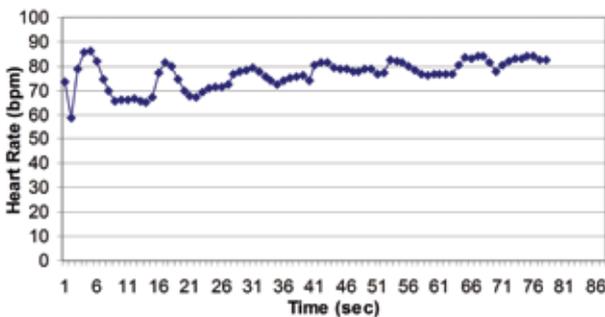


Figure 2. Deep breath test results in a 33 year old female with familial dysautonomia



control group. The RMSSD was not significantly affected by deep breathing, although it was significantly lower in the FD group both at rest and during DBT.

The LF and HF spectral components were significantly altered by DBT. LF values increased significantly from baseline in response to deep breathing in both the control group ($P < 0.001$) and the FD group ($P < 0.01$), with no significant between-group difference at either time point. Accordingly, HF values decreased significantly from baseline in response to deep breathing in both the control group ($P < 0.001$) and the FD group ($P < 0.01$), with no significant between-group difference at either time point. The LF/HF ratio increased significantly in the control group ($P = 0.001$), but the change in the FD group was not significant.

DISCUSSION

The present study investigated the link between cardiac autonomic control and deep breathing stimulation in patients with FD. The value of this test in FD has not been reported previously.

We showed that patients with FD lack the normal change in heart rate response to deep breathing. This finding was

reflected in their lower than normal values of $\Delta E/I$, HR-SD, and E/I ratio. The significantly higher MinHR during inspiration in this group indicates abnormal parasympathetic function. The autonomic dysfunction was supported by the lack of a significant change in LF/HF ratio following DBT. Power spectral analysis adds little to the DBT in detecting autonomic dysfunction in FD.

We conclude that FD is associated with a significantly disturbed response to physiological stimuli. The DBT may serve as a reliable means to quantify autonomic dysfunction in this patient population.

STUDY LIMITATIONS

The study group was small because of the low prevalence of FD. Future prospective studies with larger study groups and prolonged follow-up may shed further light on the significance of DBT in FD.

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RMSSD = root mean square successive difference

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