*International Journal of Neuropsychopharmacology* (2001), **4**, 199–206. 

SPECIAL SECTION

# Enhanced stress reactivity in paediatric anxiety disorders: implications for future cardiovascular health

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**Abstract**

The aim was to clarify the developmental nature of associations between psychiatric illness and risk for cardiovascular disease by investigating differences in cardiac functioning between youth with anxiety disorders and healthy controls. Twenty-two children meeting DSM-IV criteria for either separation anxiety disorder, overanxious disorder, panic disorder/panic attacks, or social phobia and 12 healthy controls underwent continuous electrocardiogram and respiration rate monitoring during a 15 min baseline period and 15 min of exposure to 5% $CO_2$. Heart rate (HR) and high frequency heart rate variability (HRV), a non-invasive measure of cardiac parasympathetic control, were calculated. Youth with anxiety disorders had higher and less fluctuating HR during baseline. Data also suggested that probands showed diminished overall changes in HRV during baseline and $CO_2$ inhalation relative to controls. However, as respiration rate affects HRV, these findings were confounded by changes in respiration elicited by $CO_2$ inhalation. The data suggest that youth with anxiety disorders experience an elevated and less fluctuating HR in the face of a novel situation, possibly due to a failure to appropriately modulate HRV. In adults, sustained elevations in HR in conjunction with deficient vagal modulation predicts risk for future cardiovascular disease. As such, the current data suggest that the presence of an anxiety disorder may identify youth who exhibit autonomic profiles that place them at risk for cardiac disease.

*Received 11 September 2000; Reviewed 13 December 2000; Revised 19 February 2001; Accepted 20 February 2001*

**Key words**: Paediatric anxiety disorders, cardiovascular disease, stress, heart rate, heart rate variability.

## Introduction

An expanding set of studies links psychiatric and medical illnesses. This tie appears particularly strong between psychiatric conditions involving disturbances in mood or anxiety and medical conditions involving the cardiovascular system. For example, both depression and anxiety in adults are risk factors for coronary artery disease (CAD) myocardial infarction (MI), and cardiac mortality (Barefoot and Schroll, 1996; Carney et al., 1988a, 1995; Fielding, 1991; Kawachi et al., 1994b; Musselman et al., 1998; Pratt et al., 1996). Three models have been proposed to account for these associations: (1) depression or anxiety result from stress associated with cardiac disease (Carney et al., 1999; Travella et al., 1994); (2) depression or anxiety are associated with life-style factors such as smoking that place individuals at risk for cardiovascular illnesses (Chorot and Sandin, 1994; Lovibond et al., 1986; Yeragani et al., 1990); (3) a common pathway, such as abnormalities in autonomic cardiovascular control, is involved in both emotional as well as cardiovascular diseases (Guinjoan et al., 1995; Krittayaphong et al., 1997; Lehofer et al., 1997; Mezzacappa et al., 1996). In this latter model, the association between emotional disturbance and medical illness is viewed from a developmental perspective, such that the association arises over time, possibly through the cumulative effects of chronic stress exposure on autonomic regulation or through intrinsic deficiencies in autonomic nervous system functioning.

Most consistent with this third model, there is evidence of an association between disturbances in emotion and autonomic control across the life span. Adult patients with anxiety (Friedman, 1998; Kawachi et al., 1995; Thayer et al., 1996; Yergani et al., 1993) or depressive disorders (Lehofer et al., 1997; Rechlin et al., 1994) each exhibit reductions in high-frequency heart rate variability (HF HRV), indicating a decrease of parasympathetic cardiac

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control (Carney et al., 1995; Goldberger et al., 1994; Kawachi et al., 1995; Mezzacappa et al., 1996). Similar associations emerge in studies of infants and children either at risk for future psychopathology or currently manifesting signs of psychiatric disorders (Bazhenova, 1997; Hirshfeld, 1992; Kagan et al., 1988; Mezzacappa et al., 1997; Snidman et al., 1995). Autonomic nervous system measures such as HRV and cardiac reactivity are thought to index an individual's physiological competency in the face of challenge (Porges, 1998; Porges et al., 1994). Such measures may provide a window on an individual's emotional regulation, as it relates to developmental, stress-linked models of cardiovascular disease.

Also consistent with the developmental model, there is evidence of an association between personal or familial risk for cardiovascular disease and disturbances in autonomic control across the lifespan. Among adults, reduced resting HRV predicts the severity of coronary atherosclerosis (Carney et al., 1988b; Huikuri et al., 1999) as well as mortality following MI (Cripps et al., 1991; Kleiger et al., 1987; Odemuyiwa et al., 1991; Vaishnav et al., 1994). Similarly, among children, family history of hypertension predicts reduced resting HRV (Pine et al., 1998) as well as abnormal cardiovascular reactions to various stressors (Ferrare et al., 1988; Treiber et al., 1993). These associations also involve parasympathetically mediated, high frequency (HF) components of the HRV power spectrum. This suggests that irregularity in parasympathetic cardiovascular control and/or greater cardiac reactivity, even during childhood, may indicate later risk for cardiovascular morbidity.

Taken together, these findings suggest that associations between emotional disturbance and cardiac activity during childhood may be relevant to mechanisms of cardiovascular disease, particularly since cardiac profiles during youth predict cardiac risk factor profiles in adulthood (Beckett et al., 1992; Lieberman, 1994). Despite recent emphasis on such developmental models (Cohen et al., 1998; Matthews, 2000; Porges et al., 1992), relatively few studies examine cardiac autonomic control in youth with psychiatric disorders. In a prior report, we found that both externalizing and internalizing symptoms predicted reductions in the high-frequency component of HRV (Pine, 1998). However, this report only examined resting levels of HRV in children at risk for emotional disturbance. Studies in children presenting for psychiatric treatment are therefore needed. Moreover, studies among adults find that exposure to various laboratory stressors reveal meaningful between-group differences in cardiac autonomic control beyond those seen at rest (Grimm et al., 1995; Ito et al., 1999; Piccirillo et al., 1997). Specifically, inhaling $CO_2$ enriched air is a clinically meaningful laboratory stressor for individuals with anxiety disorders as it elicits reactions similar to natural anxiety states (Beck et al., 1999; Martinez et al., 1998; Perna et al., 1999). In this paper, we studied HR at rest and during $CO_2$ inhalation in youth with anxiety disorders and in healthy controls. We reasoned that this approach would help clarify the developmental nature of associations between psychiatric illness and risk for future cardiovascular disease. We hypothesized that youth with anxiety disorders would show higher HR and lower HRV during baseline as well as an abnormal autonomic nervous system (ANS) response to $CO_2$ inhalation.

## Methods

All procedures were approved by the Institutional Review Board at New York State Psychiatric Institute. All parents provided consent and all children provided assent prior to participation.

### *Subjects*

Participants included 22 probands (9- to 18-yr-olds), with a current DSM-III-R anxiety disorder and 12 psychiatrically healthy comparisons. Probands were recruited when they presented for treatment of 1 of 4 anxiety disorders; separation anxiety disorder; overanxious disorder; panic disorder/panic attacks; or social phobia. The decision to include a range of disorders was based on two considerations: (1) the frequency of comorbity among children with anxiety disorders and (2) in adults, alterations in cardiovascular functioning that are linked to a variety of anxiety disorders. Comparisons were recruited through advertisement. All subjects were medication-free and medically healthy.

### *Psychiatric assessment*

As described elsewhere (Pine et al., 1998, 2000) subjects were evaluated through standardized parent and child interviews. All probands, comparisons, and their parents received clinical interviews by 1 of 3 child psychiatrists following standardized interviews. Psychiatrists confirmed either the presence of diagnostic criteria elicited during standardized interviews in patients or the absence of all disorders in comparisons. Probands entered the study only if both the standardized instrument and psychiatrist elicited criteria for an anxiety disorder. Comparisons entered only if instrument and psychiatrist confirmed the absence of all disorders.

### *$CO_2$ inhalation procedures*

$CO_2$ inhalation procedures in Pine et al. (1998, 2000) were used, whereby children lay in a sealed plastic canopy from

**Table 1.** Sample characteristics

| Characteristic | Proband ($n = 22$) | Comparison ($n = 12$) | Statistic |
|---|---|---|---|
| Age (yr) (mean ± s.d.)* | 12.8 ± 2.9 | 13.7 ± 2.9 | $t(29) = 1.09$; ns |
| Females (*n*, %) | 7, 58% | 6, 32% | $\chi^2 = 2.16$; ns |
| Height (cm) (mean ± s.d.)† | 154.4 ± 13.5 | 159.3 ± 12.6 | $t(27) = 0.99$; ns |
| Weight (kg) (mean ± s.d.) | 64 ± 27.6 | 53.4 ± 10.8 | $t(27) = 1.09$; ns |
| Generalized anxiety disorder | 9 | 0 | |
| Separation anxiety disorder | 4 | 0 | |
| Social phobia | 8 | 0 | |
| Panic attacks/disorder | 9 | 0 | |

* Three subjects were missing age data.
† Five subjects were missing height and weight data.

**Table 2.** Average R-R interval and HF HRV

| | Baseline | | $CO_2$ challenge | |
|---|---|---|---|---|
| Variable | Probands | Controls | Probands | Controls |
| Average R-R interval (ms) | 759.52 ± 102.38 | 885.90 ± 159.46 | 697.83 ± 92.71 | 785.84 ± 142.0 |
| HF power | 2869.16 ± 3654.18 | 5877.63 ± 4179.15 | 3226.81 ± 4903.1 | 4632.5 ± 3541.83 |

All data are expressed as mean ± s.d.
HF, high frequency.

which they could escape by lifting a latch. While monitored for continuous EEG reading, subjects breathed room air for 15 min followed by 15 min of 5% $CO_2$ inhalation. Electrocardiogram (EKG) signals were passed into a microcomputer after being amplified on a Grass Model 7 polygraph. The EKG signal was passed into a K&M RR2CI R-R interval pre-processor that measures R-R intervals to an accuracy of 0.1 ms. This pre-processor means measures the interval between input waveform peaks using a diode-feedback op-amp circuit configured with a Bessel type (12 db/octave) high-pass filter of 5 Hz and a first order low-pass filter at 50 Hz. The accuracy of this instrument has been well validated (Myers, 1984). Artifacts were identified using procedures outlined by Bernston et al. (1990). HRV was indexed as the high frequency (HF) (0.15–0.50 Hz) band of the HRV power spectrum. Power spectral analyses of the R-R interval time series were conducted using an interval method for computing Fourier transforms similar to that described by DeBoer et al. (1984). As in prior studies from our research group (Sloan et al., 1994), spectra were calculated on 60-s epochs using the same interval method for computing Fourier transforms. Before computing transforms, the mean of the R-R interval was subtracted form each interval and the resultant series was filtered with a Hanning window. These R-R data were then submitted to a fast Fourier transform. Spectra were calculated on 60-s epochs of artifact-free R-R interval data. Epochs with artifacts were treated as missing data. Respiratory rate was measured using spirometery. Values were averaged for 30-s epochs. Artifacts were detected using two procedures. First, non-physiological values were removed using preset criteria. Secondly, raw data and data-plots were inspected to ensure that all non-physiological values had been removed. Data-points 2 s.d.s above the mean for a subject during an epoch were reviewed without knowledge of the clinical status by three investigators and were either removed or retained based on consensus. Values were removed when adjacent breaths were read as one breath. In total, less than 1% of the data contained outliers.

### *Data analysis*

We used mixed effect models to carry out the data analysis. Subjects were entered in to the models as random effects. HR, HRV, and respiratory rates were treated as the dependent repeated measures, and psychiatric variables were treated as independent variables.

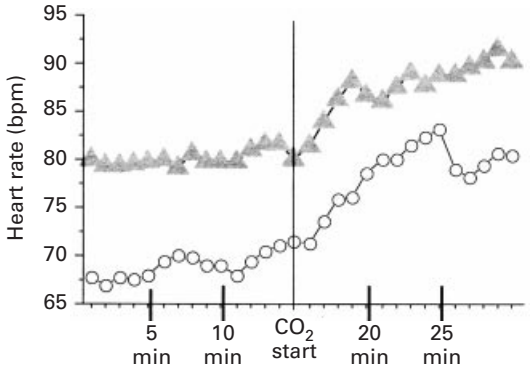


**Figure 1.** Minute-by-minute heart rate during 15 min baseline and 15 min $CO_2$ challenge by group. ▲, Probands; ○, healthy controls.

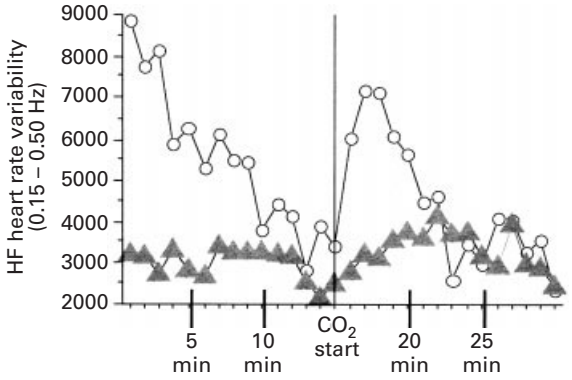


**Figure 2.** Minute-by-minute HF heart rate variability during 15 min baseline and 15 min $CO_2$ challenge by group. ▲, Probands; ○, healthy controls.

Variables such as age and gender also were considered in the models to account for their possible confounding effects. Because respiration rate influences vagal modulation of the heart (Brown et al., 1993; Myers, 1984), we also controlled for respiration rate when analysing HRV. We log-transformed HRV to correct for skewness. Respiration-corrected HRV measures were obtained as the residuals from the regression of log HRV on the respiratory rate. All analyses were performed using a 0.05 two-tailed significance level. The SAS System, release 7.0 (SAS, Institute, Inc., Cary, NC), was used to perform the analyses. Three subjects did not have usable respiration rate data (all 3 from the proband group). This report is based on the remaining 31 subjects.

## Results

### *Sample characteristics*

Table 1 summarizes sample characteristics. The groups did not differ on age, ratio of males to females, weight, or height. However, because these variables are associated with differences in cardiovascular activity, they were controlled for in the subsequent analyses.

### *Baseline HR and HRV*

Average R-R interval and HF power are displayed in Table 2.

Averaged across the 15 min baseline period, children with anxiety disorders had significantly higher HR [$M = 80.27 \pm 10.0$ vs. $M = 70.1 \pm 12.2$ bpm; $t(398) = 3.07$; $p < 0.01$] after controlling for age and sex effects. Probands also showed less overall HRV during baseline [$M = 2869.16 \pm 3654.2$ vs. $M = 5877.63 \pm 4179.1$; $t(408) = 3.18$; $p = 0.01$] when age and sex were entered as covariates. However, after also controlling for respiration rate, as well as age and sex, there was no significant group difference in HRV. Because the groups differed on baseline HR values, baseline HR serves as a covariate in subsequent analyses of reactivity.

### *HR during baseline and challenge*

After controlling for age, sex, and baseline differences, there was a 3-way group × time × $CO_2$ inhalation interaction [$F(2,752) = 24.05$; $p = 0.0001$] for HR, suggesting differential effects of the baseline period and $CO_2$ inhalation on the two groups over time (see ANOVA Table 1 below). However, when the data was analysed for the $CO_2$ period only, there was no group difference in the changes in HR over time [$F(1,324) = 0.12$; $p = 0.72$], indicating that both groups had similar HR responses to $CO_2$ inhalation. When the data was analysed for the baseline period only, there was a group difference in the changes in HR over time [$F(1,408) = 6.47$; $p < 0.01$], indicating that both groups had different patterns of HR activity during baseline. Figure 1 depicts minute-by-minute HR reactivity during baseline and $CO_2$ inhalation by group. Taken together, the data suggest that relative to healthy subjects, probands demonstrated comparable increases in HR during the stressor period and less fluctuations in HR during the baseline period.

**ANOVA Table 1.** HR during baseline and $CO_2$ challenge

| | d.f. | *F* value | *p* value |
|---|---|---|---|
| Group × period | 1/752 | 5.20 | 0.02 |
| Group × time | 1/752 | 10.72 | 0.001 |
| Group × time × period | 2/752 | 24.05 | 0.0001 |

### *HRV during baseline and challenge*

For HRV, there was a main effect of time on group responses after controlling for sex, age, and baseline differences (see ANOVA Table 2 below). Figure 2 depicts group differences in minute-by-minute HRV reactivity during baseline and $CO_2$ inhalation. Overall, probands demonstrated less change over time in HRV, relative to healthy subjects. Specifically, probands showed only small adjustments in HF power during $CO_2$ inhalation. In contrast, healthy comparisons exhibited a robust decrease in HRV over the course of the baseline period and in the early phases of $CO_2$ inhalation, between minutes 3 and 8 of $CO_2$ challenge (represented as minutes 18–23 of Figure 2, which depicts the total 30 min paradigm). However, when respiration rate was included as a covariate, the group differences were no longer significant.

**ANOVA Table 2.** HF HRV during baseline and $CO_2$ challenge

| | d.f. | *F* value | *p* value |
|---|---|---|---|
| Group × period | 1/758 | 0.70 | 0.40 |
| Group × time | 1/758 | 4.19 | 0.04 |
| Group × time × period | 2/758 | 0.73 | 0.48 |

## Discussion

In this study, we examined HR and HRV during baseline and in response to a mild stressor, 5% $CO_2$ inhalation, among children and adolescents with anxiety disorders and healthy comparisons. Cardiovascular measures in children and adolescents with anxiety disorders differed from those of healthy comparisons during baseline and in response to challenge.

During the 15-min baseline, probands had a higher average HR compared to healthy individuals, controlling for age and sex effects. This finding is consistent with earlier data showing that psychiatric symptoms in youth predict reduced HRV during rest (Pine, 1998) as higher HR is often associated with parasympathetic withdrawal. However, in this report, once we controlled for respiration rate, there was no group difference in resting levels of HRV. Thus, in the prior report from our group, both parent ratings of anxiety as well as behaviour symptoms inversely correlated with resting HRV whereas in the current study, children presenting for treatment of frank anxiety disorders did not exhibit different levels of resting HRV compared to controls. There are two primary hypotheses to account for these data: (1) with the addition of respiration rate to the data analysis of our current study, there is not adequate statistical power to test for differences in HRV and (2), because the baseline period prior to a *respiratory* challenge may elicit respiration changes and respiration rate acts as a 'gate' on the vagal control for the heart, group differences in resting HRV may be obscured by variability in respiration rate.

Such associations between behaviour and resting HR activity may arise even earlier than the school-age years. Kagan et al. (1988) found that pre-schoolers with inhibited temperament, who are at risk for anxiety disorders (Rosenbaum et al., 1993), also exhibit higher and less variable resting HR (Kagan et al., 1988; Snidman et al., 1995). Of note, group differences in the current study, as in Kagan et al. (1988), may reflect probands' cognitive appraisal of the novel laboratory situation as potentially threatening rather than underlying group differences in cardiac functioning. To further consider this possibility, it will be important in the future to monitor cardiovascular indices in multiple experimental contexts, including the home.

Beyond such mean differences in HR at baseline, children and adolescents with anxiety disorders in the current study also exhibited an altered pattern of cardiovascular activity. Compared to healthy controls, children and adolescents with anxiety disorders showed less overall fluctuation in HR during baseline. Furthermore, although the variability of the respiration data makes interpretation of the HRV results inconclusive, the data nonetheless suggest that probands also had an altered pattern of HRV over the course of the 30 min study. As seen among adults, the physiological response of healthy children and adolescents to $CO_2$ inhalation involves a marked change in HF HRV (George et al., 1989). This change most prominently involves a steep reduction in HRV early in the exposure to the stressor. Children and adolescents with anxiety disorders, in contrast, exhibited no such changes. In this group, during the baseline and stressor periods, vagal modulation of the heart varied less than in comparisons.

From a developmental perspective, these findings are consistent with the view of shifts in cardiac vagal control as an appropriate response to changing environmental demands (Huffman et al., 1998; Porges, 1998). The data suggest that children and adolescents with anxiety disorders, who may generalize maladaptive behavioural responses to many situations (Chorpita, 1998), show a higher resting and less variable HR in the face a novel situation – the laboratory study, possibly due to a failure to appropriately modulate HF HRV. A higher HR in conjunction with a deficient vagal modulation during stress, as found in the current study, represents an autonomic pattern associated with risk for future CAD (Airaksinen et al., 1987; Jiang et al., 1993). As such, the current data suggest that the presence of an anxiety

disorder may identify youth who exhibit autonomic profiles that place them at risk for cardiac disease.

Given the significant adult comorbidity of psychiatric symptoms and CAD (Barefoot et al., 1996; Boscario and Chang, 1999; Chorot and Sandin, 1994; Kawachi et al., 1994a; Kubzansky et al., 1998; Musselman et al., 1998), coupled with the predictive relationship between child and adult anxiety disorders, the current data on cardiac reactivity in paediatric anxiety disorders raise the possibility that effective treatments for paediatric anxiety disorders may reduce risk for future heart disease. Moreover, the current data support the hypothesis that physiological components of anxiety disorders may operate across development, potentially contributing to adult cardiovascular illness. As such, the findings are consistent with developmental hypotheses on associations between abnormalities in emotion regulation and processes linked to cardiovascular disease (Cohen et al., 1998; Matthews, 2000; Porges et al., 1992).

There are several limitations of the study. The relationship between HRV, HR, respiratory rate, and anxiety disorders needs to be examined further. The stressor we chose, $CO_2$ inhalation, directly influences breathing rate (even perhaps during a baseline period when subjects might anticipate a change in air quality) and respiration rate influences cardiac vagal modulation. In addition, as previously suggested, for probands, the anticipation of a potentially stressful unknown event (e.g. a laboratory study involving exposure to $CO_2$) might have been more stressful and/or salient than it was to the healthy controls. Thus, the probands' elevated HR response might have resulted from the significance of the stimuli to this group rather than from alterations in cardiac activity per se. To study more fully associations between anxiety disorders and HRV as well as HR during stress, group differences in cardiac activity should be assessed during controlled breathing as well as in response to a range of stress paradigms, including various physiological as well as psychological probes. These might include exercise, the cold pressor test, and the Stroop colour–word-matching task. Children with anxiety disorders may exhibit abnormal reactions to a range of stressors or may show abnormal responses only in the face of particular stressors. Finally, our results are based on a small sample and need to be replicated with larger numbers.

## Acknowledgements

This project was supported by NIMH Center Grant MH-43878 to the Center to Study Youth Anxiety, Depression, and Suicide; an NIMH Scientist Development Award to R.P.S. (MH-01035); and an NIMH Scientist Development Award for Clinicians to D.S.P. (MH-01309).

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