Letter to the Editor

Psychotherapy and Psychosomatics

Received: April 14, 2010
Accepted: July 4, 2010
Published online: November 18, 2010

Psychother Psychosom 2011;80:62–64
DOI: 10.1159/000318781

Reduced Cardiac Autonomic Flexibility Associated with Medically Unexplained Somatic Complaints in the Context of Internalizing Symptoms in a Preadolescent Population Sample: The TRAILS Study

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Medically unexplained somatic complaints (MUSC; e.g. headaches, abdominal pain) are common in youths and may lead to increased medical consumption, poorer academic attainment and future somatic ill health [1–3]. MUSC are strongly associated with both current and future anxiety and depression symptoms [3, 4], which all are assumed to partly reflect the independent expression of underlying distress through bodily versus psychological symptoms, respectively [5].

Dysfunction of the autonomic nervous system as one of the major physiological stress systems has been suggested as an important mechanism in MUSC [6–10]. However, the findings on the association between MUSC and cardiac autonomic measures are still inconsistent [11–14]. The use of small-sized samples may have contributed to this. Presently, we lack large-sized population studies using a dimensional approach regarding MUSC, especially in youths, hence pointing to early autonomic risks [2, 15]. Indicators of cardiac autonomic inflexibility or dysfunction, such as reduced high-frequency heart rate variability (HF-HRV; indicating vagal activity) and, particularly, baroreflex sensitivity (BRS; indicating the flexible regulation of autonomic balance between the vagal and sympathetic nervous system) have rarely been investigated [6, 8, 9, 16]. Moreover, research into patterns of physiological functioning that discriminate between MUSC and anxiety and depression symptoms is sparse [2, 4]. The potentially confounding effects of co-occurring internalizing symptoms, which may have served to inflate effect sizes, mask effects or even influence the direction of effects, have often been neglected [17].

We investigated the relationship of dimensionally measured MUSC with HF-HRV and BRS in a large preadolescent population cohort, taking into account co-occurring internalizing symptoms. We expected to find reduced autonomic flexibility (lower HF-HRV and BRS) in association with MUSC. In addition, for the first time, we report on the association between BRS and anxiety symptoms in youths [18; for HF-HRV and depression symptoms see 19–21].

The participants were 921 10- to 13-year-old Dutch preadolescents (53.1% girls; 11.5 ± 0.5 years) from the population cohort TRacking Adolescents' Individual Lives Survey [21–23]. Written informed consent was obtained from the parents; children participated voluntarily. The study was approved by the medical ethics committee.

Internalizing symptoms (i.e. anxiety, depression and MUSC, including abdominal pain, headaches, nausea and stomachache) were assessed by the Child Behavior Checklist (CBCL, parent report) and Youth Self-Report (YSR, childreport), using DSM-IV scales [1, 24, 25]. Each informant may provide a specific aspect of the construct being measured, as agreement between their judgements is generally low ($r = 0.21–0.34$, $p < 0.001$; [25, 26]). Pearson's correlations between the 3 respective CBCL and YSR scales were moderate ($r = 0.30–0.60$, $p < 0.001$). Internalizing problems were largely in the nonclinical range (97.5%). Externalizing problem scale scores across the DSM-IV-based attention deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder scales were calculated and used as a covariate.

Continuous noninvasive HR and systolic blood pressure (BP) measurements of 4 min in the supine position were conducted during spontaneous breathing [23]. HF-HRV (0.15–0.40 Hz, ln [ms^2]) and BRS (0.07–0.14 Hz, ln [ms/mm Hg], coherence 0.3) were calculated using power spectral analysis [22, 27–29]. A lower BRS points towards reduced responsiveness of the autonomic nervous system to regulate short-term BP changes through HR variations, reflecting low vagal and/or high sympathetic influences on the heart ($r_{HF\text{-}HRV\text{-}BRS} = 0.65$, $p < 0.001$, [16]). We additionally calculated BRS2 with 0.5 coherence, as generally applied (n = 522; [22, 27]). The respiration rate was not accounted for since the breathing rates of youngsters commonly fall within the HF range [30]. We have shown a satisfactory short-term test-retest reliability of our autonomic nervous system measurements [27].

Linear regression analyses were conducted separately for CBCL- and YSR-based ratings, with HF-HRV and BRS as separate outcome variables, and all internalizing subscales entered simultaneously as predictor variables, adjusted for confounders (table 1). The analyses were repeated for BRS2 to investigate concurrent validity. The tests were 2-tailed using $p < 0.05$.

Table 1 shows that in boys and girls MUSC were significantly associated with lower supine HF-HRV (YSR) and BRS (YSR, CBCL boys only). The results on BRS2 were similar, with a negative association between MUSC and BRS2 (YSR: $B = -0.12$, $p < 0.05$; CBCL boys only: $B = -0.17$, $p < 0.05$, n = 239), supporting concurrent validity. Depression symptoms (YSR) were signifi-

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0033–3190/11/0801–0062$38.00/0

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Table 1. Linear regression analyses with HF-HRV and BRS as separate outcome variables and MUSC and potential confounders as predictor variables

Predictors	HF-HRV				BRS			
	CBCL		YSR		CBCL		YSR	
	B	p	B	p	B	p	B	p
Main effect model	[1]		[2]		[3]		[4]	
Gender	0.08	<0.05	0.07	<0.05	0.12	<0.001	0.12	<0.001
Age	–0.16	<0.001	–0.16	<0.001	–0.02	0.52	–0.03	0.42
Physical activity	0.02	0.62	0.03	0.37	0.01	0.82	0.02	0.62
SBP	–0.09	<0.01	–0.09	<0.01	–0.10	<0.01	–0.10	<0.01
Externalizing problems	0.07	0.06	0.08	0.05	0.03	0.45	0.01	0.85
Anxiety symptoms	–0.09	<0.05	–0.01	0.75	0.02	0.66	0.01	0.76
Depression symptoms	–0.03	0.56	0.01	0.76	–0.04	0.39	0.01	0.76
MUSC	–0.06	0.13	–0.09	<0.05	–0.05	0.14	–0.10	<0.01
Interaction effect models	[5]		[6]		[7]		[8]	
Gender × anxiety symptoms	–0.02	0.86	–0.20	0.10	–0.01	0.98	–0.18	0.17
Gender × depression symptoms	0.04	0.72	Boys: 0.15 Girls: –0.05	<0.05[9] 0.39	0.18	0.16	0.19	0.16
Gender × MUSC	0.02	0.85	–0.02	0.86	Boys: –0.12 Girls: 0.01	<0.05[10] 0.95	0.14	0.23

Physical activity = self-reported frequency of performing sports (e.g. swimming, playing soccer; 0 = almost never to 4 = 6–7 times a week). Full model: [1] $F_{(8,900)} = 6.6$, $p < 0.001$, $R^2 = 4.7\%$; [2] $F_{(8,903)} = 6.1$, $p < 0.001$, $R^2 = 4.3\%$; [3] $F_{(8,900)} = 3.8$, $p < 0.001$, $R^2 = 2.4\%$; [4] $F_{(8,903)} = 4.5$, $p < 0.001$, $R^2 = 3.0\%$; [5] $F_{(11,897)} = 4.8$, $p < 0.001$, $R^2 = 4.4\%$; [6] $F_{(11,900)} = 4.8$, $p < 0.001$, $R^2 = 4.4\%$; [7] $F_{(11,897)} = 3.1$, $p < 0.001$, $R^2 = 2.5\%$; [8] $F_{(11,900)} = 3.8$, $p < 0.001$, $R^2 = 3.1\%$; [9] boys: $F_{(7,420)} = 6.3$, $p < 0.001$, $R^2 = 8.3\%$; [10] boys: $F_{(7,417)} = 1.9$, $p = 0.07$, $R^2 = 3.0\%$.

cantly associated with higher supine HF-HRV in boys only and not with BRS/BRS2. Anxiety symptoms (CBCL) were significantly associated with lower supine HF-HRV in boys and girls, and not with BRS/BRS2.

Our study suggests reduced autonomic flexibility (hyperarousal) in relation to MUSC, independent of co-occurring internalizing symptoms and other important confounders. This work extends previous findings of reduced autonomic flexibility in adult patients with MUSC [14, 31, 32] to a large nonclinical pediatric population sample with generally mild symptoms. We provide additional evidence to an earlier study, which reported a negative association between cardiac measures (HRV, BRS) and somatic-depressive symptoms (e.g. lack of appetite, overtiredness, [20]), both studies tapping into different aspects of MUSC. The lack of an association between BRS and anxiety symptoms remains elusive. Albeit speculative, it is plausible that the reduced baroreflex regulation of sympathovagal balance primarily finds its expression in MUSC as compared to cognitive-affective symptoms [20], since baroreflex dynamics primarily involve (sub)medullary brain stem mechanisms that are of vital importance in the organisms' adaptation via primary motor and somatic functions [16, 28]. More studies are needed to investigate the different aspects of MUSC in relation to autonomic functioning.

The cross-sectional nature of this study prevents directional or causal interpretations. Further limitations are the use of resting measurements only and not accounting for respiratory irregularities, which may have weakened associations. The small effects should also be considered in light of the mild symptoms within a heterogeneous non clinical sample. The foremost value of this study, however, lies in the detection of early risks of autonomic dysfunction. Although BRS is a sophisticated measure of autonomic balance, a future investigation of the interaction with underlying central mechanisms would add to our understanding of the neurophysiology of MUSC.

This study contributes to a neurobiological rationale for the clinical use of anxiety-reducing therapeutic interventions in MUSC, particularly biofeedback and relaxation training, which directly aim at lowering physiological arousal [33]. We recommend to take account of MUSC in anxiety and depression research in relation to cardiac autonomic functioning, as findings may differ according to the magnitude of co-occurring MUSC.

Acknowledgments

This research is part of the TRacking Adolescents' Individual Lives Survey. The participating centers of TRAILS include various departments of the University Medical Center and University of Groningen, the Erasmus University Medical Center Rotterdam, the University of Utrecht, the Radboud Medical Center Nijmegen and the Parnassia Bavo group, all in the Netherlands. The European Research Advisory Board (EA 0609) gave funding to K.G.-L. We are grateful to all children, their parents and teachers who participated in this research and to everyone who worked on this project and made it possible.

Conflicts of Interest

No conflicts of interest to declare.

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