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Review

Heart rate variability in individuals with Down syndrome – A systematic review and meta-analysis

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ABSTRACT

Introduction: Down syndrome (DS) results in many changes, including dysfunction in cardiac autonomic modulation. Heart rate variability (HRV) analysis evaluates the autonomic function and it is a predictor of adverse cardiovascular events.

Objective: To present results of a systematic review and a meta-analysis about heart rate variability in individuals with DS.

Method: A systematic review was performed on PubMed, PubMed Central and Web of science databases. We included articles that exhibited all the terms: "Down Syndrome", "heart rate variability", "autonomic nervous system", "autonomic dysfunction" and "cardiac autonomic modulation". We conducted the meta-analysis to compare "DS" to "controls" during rest. Random effects models were used, as were appropriate tests for heterogeneity.

Results: From 271 studies, 13 were included in our review. These are conducted with volunteers from a wide age range, of either gender, and not taking medications. Meta-analysis displayed that there were no significant differences between the groups at rest, except the RMSSD, which revealed a significant ($Z = -2.80$, $p = 0.005$) main effect (Hedge's $g = -0.55$, 95% CI [−0.93; −0.16]), indicating difference in individuals with DS compared with controls.

Conclusion: There is autonomic dysfunction in individuals with DS, which may or may not be expressed at rest, but it is usually demonstrated in an autonomic task. Meta-analysis specified that there was no significant alteration between DS and the controls during rest, except RMSSD index which was lower in DS than controls.

PROSPERO: CRD42017068647.

1. Introduction

Down syndrome (DS) is the most frequently occurring chromosomal abnormality in humans (trisomy of whole or part of chromosome 21), affecting about one in every 750 live births in all populations (Kazemi et al., 2016; Kazemi et al., 2017). Frequently, individuals with DS present muscle hypotonia, hypothyroidism, gastrointestinal and pulmonary disorders, leukemia, delayed psychomotor and neurological development, audio vestibular and visual impairment, early-onset Alzheimer's disease, dementia, and congenital heart disease (Van Gameren-Oosterom et al., 2012; Fernhall et al., 2013).

Current studies indicate that individuals with DS exhibit a dysfunction in autonomic cardiac modulation, when compared with non-disabled control subjects. Overall, individuals with DS have low physical work capacity, chronotropic incompetence and significantly reduced heart rate and blood pressure responses to autonomic tasks, such as exercise and the tilt test (Iellamo et al., 2005; Fernhall et al., 2013; Bunsawat et al., 2015). According to Fernhall and Otterstetter (2003)

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the dysfunction in autonomic cardiac modulation in DS could be related to depressed sympathetic tone or a response of incomplete vagal withdrawal.

Under typical conditions, the chronotropic state of the heart is entirely regulated by the sinoatrial (SA) node, which is directly innervated by the autonomic nervous system (ANS) that can be split into two efferents; parasympathetic (vagal) and sympathetic (phrenic) (Draghici and Taylor, 2016). Adjustments in at least one of those efferents can be considered an autonomic dysfunction, which may represent an important adverse factor, since the autonomic functioning controls part of the internal functions of the body and, it can be associated with increased risk of early mortality and morbidity (Task Force, 1996; Baynard et al., 2004; Angiovlasitis et al., 2011).

One of the ways to assess the ANS is heart rate variability (HRV), which is a simple, inexpensive and noninvasive measure of the balance between sympathetic and parasympathetic mediators of heart rate (Karim et al., 2011; Draghici and Taylor, 2016). It defines the fluctuation of the intervals between consecutive heart beats (RR intervals) and these are related to the stimuli of the ANS on the SA node (Task Force, 1996; Vanderlei et al., 2009).

HRV offers an important index as a potential marker of physiological stress and health for organism functions associated with adaptability and health (Draghici and Taylor, 2016). It has been considered a predictor of adverse cardiovascular events in different conditions (Task Force, 1996; Vanderlei et al., 2009; Karim et al., 2011). Understanding these topics specifically in DS can further information about the influence of this syndrome in the ANS function and provide support to improve therapies in order to enhance the quality of life of these individuals. To the best of our knowledge, there is neither meta-analysis nor revision undertaken jointly in this manner.

Considering the above interpretations, the purpose of this study is to present results of a systematic review and a meta-analysis about heart rate variability in individuals with DS.

2. Methods

This review was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, so providing a comprehensive framework which accurately assesses indicators of quality and risk of biases of included studies (Hutton et al., 2015). The protocol for this review was previously registered with PROSPERO, number registration: CRD42017068647.

2.1. Eligibility criteria

At the outset, the titles of articles were evaluated, and then their abstracts were screened, according to some conditions. Articles included: (1) a diagnosis of Down syndrome, (2) HRV analysis, (3) studies that included autonomic nervous system, (4) studies that aimed to study cardiac autonomic modulation. Articles were excluded if they were: (1) not data-based (e.g. books, theoretical papers, or secondary reviews), (2) not written in the English language, (3) had populations not explicitly identified as having a diagnosis of DS, or (4) did not include HRV analysis.

2.2. Information sources and search

This appraisal was based on a systematic search of published articles available through July 2017. The article search was performed in Medline/PubMed, PubMed Central- PMC, and Web of Sciences databases - WOS, through keywords that must be in all fields (Table 1).

In brief, reference lists of retrieved studies were comprehensively searched for with additional relevant studies (Arab et al., 2016). Keywords and combinations of keywords were used to search the electronic databases and were organized following the Population Intervention Comparison Outcome (PICO) model. All identified studies were

Table 1
Systematic search of articles available.

	PubMed		PubMed central		Web of science	
	Syntax	Results	Syntax	Results	Syntax	Results
1st Search	Down Syndrome [All Fields] AND "heart rate variability" [All Fields]	08	Down Syndrome [All Fields] AND "heart rate variability" [All Fields]	88	Down Syndrome [All Fields] AND "heart rate variability" [All Fields]	21
2nd Search	Down Syndrome" AND "heart rate variability" OR "autonomic nervous system" = ("autonomic nervous system" [All Fields] AND "Down Syndrome" [All Fields]) AND "heart rate variability" [All Fields]	03	Down Syndrome" AND "heart rate variability" OR "autonomic nervous system" = ("autonomic nervous system" [All Fields] AND "Down Syndrome" [All Fields]) AND "heart rate variability" [All Fields]	28	Down Syndrome" AND "heart rate variability" OR "autonomic nervous system" = ("autonomic nervous system" [All Fields] AND "Down Syndrome" [All Fields]) AND "heart rate variability" [All Fields]	0
3rd Search	"Down Syndrome" [All Fields] AND "autonomic dysfunction" = "autonomic dysfunction" [All Fields] AND "Down Syndrome" [All Fields]	12	"Down Syndrome" [All Fields] AND "autonomic dysfunction" = "autonomic dysfunction" [All Fields] AND "Down Syndrome" [All Fields]	85	"Down Syndrome" [All Fields] AND "autonomic dysfunction" = "autonomic dysfunction" [All Fields] AND "Down Syndrome" [All Fields]	14
4th Search	"Down Syndrome" [All Fields] AND "cardiac autonomic modulation" = "cardiac autonomic modulation" [All Fields] AND "Down Syndrome" [All Fields]	03	"Down Syndrome" [All Fields] AND "cardiac autonomic modulation" = "cardiac autonomic modulation" [All Fields] AND "Down Syndrome" [All Fields]	06	"Down Syndrome" [All Fields] AND "cardiac autonomic modulation" = "cardiac autonomic modulation" [All Fields] AND "Down Syndrome" [All Fields]	03