

## Sitting intolerance: A new disease entity in children and adolescents

Sitting intolerance refers to a series of symptoms (e.g., dizziness, headache, blurred vision, chest tightness, nausea, abdominal pain, numbness, and syncope) induced by sedentariness or a sudden transition from a supine position to a sitting position.<sup>1,2</sup> Many investigations regarding the pathogenesis, clinical manifestation, diagnosis, and treatment of orthostatic intolerance have been conducted in recent years, but little is known about these issues with respect to sitting intolerance among children and adolescents. Notably, sitting syncope is not rare among adults with a history of syncope. In a study of 111 adult patients, Khadilkar et al.<sup>1</sup> found that 16 experienced syncopes only in a sitting position and 23 experienced syncopes in multiple positions (including sitting). In a study of 62 adult patients, Graham et al.<sup>3</sup> found that 19% had sitting syncope. In a study of 3877 adult patients, Sorajja et al.<sup>4</sup> reported that 9.8% of patients experienced syncope while driving in the sitting position. Furthermore, sitting syncope is not unusual among children and adolescents. In a large-scale multi-center cross-sectional study, Tao et al.<sup>5</sup> found that children and adolescents were vulnerable to sitting intolerance. Specifically, 66 of 686 young participants had symptoms of sitting intolerance. The findings by our team indicate that the incidence of sitting intolerance symptoms among children and adolescents may reach 9.6%.<sup>5</sup> The diagnostic criteria for pediatric sitting intolerance were not established until 2020<sup>5</sup>, and the pathogenesis remains unclear and may be multifactorial. To our knowledge, there has been less research concerning the prevention and treatment of sitting intolerance.

Sitting intolerance involves similar hemodynamics to the hemodynamics of orthostatic intolerance. Under normal circumstances, sedentariness or a sudden change from a supine position to a sitting position reduces venous return to the heart, stimulating pressoreceptors, and the sympathetic nervous system, leading to rapid inhibition of the parasympathetic nervous system.<sup>6–9</sup> Subsequently, humoral

regulation may be involved. In terms of orthostatic intolerance, especially postural tachycardia syndrome, numerous studies of humoral regulation have revealed that abnormalities in endogenous hydrogen sulfide levels,<sup>10,11</sup> renin-angiotensin-aldosterone system (RAAS) activation,<sup>12,13</sup> catecholamine levels,<sup>14</sup> endothelin-1 levels,<sup>15</sup> and nitric oxide levels<sup>16</sup> contribute to the pathogenesis of orthostatic intolerance. These humoral mechanisms underlying orthostatic intolerance may also contribute to the development of sitting intolerance, but further studies are needed. The combined effects of nervous and humoral regulation could lead to an increased heart rate and elevated blood pressure. Importantly, any regulatory abnormality may lead to sitting intolerance.

The similar underlying mechanisms imply similar risk factors for sitting intolerance and orthostatic intolerance. These risk factors may include, insufficient intake of fluid and saline, changes in the level of estrogen, and exposure to a muggy environment. Wang et al.<sup>17</sup> reported that an increase in sleeping time by 1 h per day would lead to a 37.3% reduction in the risk of sitting tachycardia syndrome (STS).<sup>17</sup> This finding might be explained by sleeping deprivation-induced dysfunction in the autonomic nervous system, leading to the abnormal secretion of endocrine hormones such as RAAS components and catecholamine.<sup>17–19</sup>

The subtypes of orthostatic intolerance generally include vasovagal syncope, postural tachycardia syndrome, and so forth.<sup>20</sup> Similarly, sitting intolerance can be divided into STS and sitting hypertension.<sup>5</sup> Tao et al.<sup>5</sup> performed an active sitting test among participants in their study, and the findings revealed an association between hemodynamic changes and symptoms of sitting intolerance among children and adolescents. On the basis of those findings, Tao et al.<sup>5</sup> proposed the first set of diagnostic criteria for STS and sitting hypertension. For children and adolescents who

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exhibited symptoms of orthostatic intolerance within 3 min after shifting from a supine position to a sitting position during an active sitting test, STS should be suspected when the heart rate is increased by  $\geq 25$  beats/min, whereas sitting hypertension should be suspected when the blood pressure is elevated by  $\geq 20/20$  mmHg.<sup>5</sup> However, Tao et al.<sup>5</sup> found no obvious relationship between sitting intolerance and sitting hypotension. The possible explanation may be the facts such as low incidence of sitting hypotension in younger individuals, and/or less blood transfer to lower extremities while sitting, and so forth.

The recommendations by Tao et al.<sup>5</sup> indicate that the diagnosis of sitting intolerance should be based on relevant predisposing factors (e.g., sedentariness, sudden change from a supine position to a sitting position, and long-term sitting, and so forth); clinical manifestations, such as sitting intolerance; and the exclusion of cardiac, neurologic, or metabolic diseases. The most common clinical manifestations of pediatric sitting intolerance are dizziness (74%), blurred vision (21%), headache (15%), and other complaints (e.g., chest tightness, nausea, abdominal pain, numbness, syncope, and so forth). The most important consideration is the outcome of the active sitting test. The interpretation of sitting test results should be based on the diagnostic criteria established by Tao et al., as mentioned above.

There has been less research concerning the therapeutic regimen for sitting intolerance. Whether measures for the prevention and treatment of orthostatic intolerance (e.g., counterpressure actions, oral rehydration salts, midodrine hydrochloride, and/or adrenoceptor blockers) may also be effective for individuals with STS needs future investigation. Also, the prevention and treatment of sitting intolerance merit further studies.

Sitting intolerance is a new disease entity with a relatively high incidence, which has received less attention. It expanded the disease spectrum of pediatric syncope. Recently, the incidence of sitting intolerance has increased, presumably because of prolonged sitting among children. Sitting intolerance seriously affects the quality of life of affected individuals. Thus far, the epidemiological characteristics and exact incidence of sitting intolerance remain unclear. Therefore, multi-center studies across countries are needed to determine the epidemiological characteristics of this disease, which will, of course, provide insights concerning its treatment and prevention. In terms of pathogenesis, the underlying hemodynamic changes and humoral mechanisms have not been elucidated. Thus, laboratory investigations are needed at the molecular, cellular, pathophysiological, electrophysiological, and genetic levels; and through such studies, the statuses of body fluids, vascular function, inflammation, immune responses, and symp-

thetic nerve activity should be elucidated. With respect to diagnosis, the active sitting test is a critical test of sitting intolerance; and it should be used when sitting intolerance is suspected. Thus far, advances in diagnosis are necessary; and these progress will be made along with further clinical reports of sitting intolerance. Finally, therapeutic options for sitting intolerance are limited right now, and there is a critical need to discover new drug targets and treatment options.

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### CONFLICT OF INTEREST

Junbao Du is a member of the *Pediatric Investigation* editorial board.

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