

## **Chronic Fatigue Syndrome: Exercise Performance Related to Immune Dysfunction**

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### **Abstract and Introduction**

#### **Abstract**

**Purpose:** To date, the exact cause of abnormal exercise response in chronic fatigue syndrome (CFS) remains to be revealed, but evidence addressing intracellular immune deregulation in CFS is growing. Therefore, the aim of this cross-sectional study was to examine the interactions between several intracellular immune variables and exercise performance in CFS patients.

**Methods:** After venous blood sampling, subjects (16 CFS patients) performed a maximal exercise stress test on a bicycle ergometer with continuous monitoring of cardiorespiratory variables. The following immune variables were assessed: the ratio of 37 kDa Ribonuclease (RNase) L to the 83 kDa native RNase L (using a radiolabeled ligand/receptor assay), RNase L enzymatic activity (enzymatic assay), protein kinase R activity assay (comparison Western blot), elastase activity (enzymatic-colorimetric assay), the percent of monocytes, and nitric oxide determination (for monocytes and lymphocytes; flow cytometry, live cell assay).

**Results:** Forward stepwise multiple regression analysis revealed 1) that elastase activity was the only factor related to the reduction in oxygen uptake at a respiratory exchange ratio (RER) of 1.0 (regression model:  $R^2 = 0.53$ ,  $F(1,14) = 15.5$ ,  $P < 0.002$ ; elastase activity  $P < 0.002$ ); 2) that the protein kinase R activity was the principle factor related to the reduction in workload at RER = 1.0; and 3) that elastase activity was the principle factor related to the reduction in percent of target heart rate achieved.

**Conclusion:** These data provide evidence for an association between intracellular immune deregulation and exercise performance in patients with CFS. To establish a causal relationship, further study of these interactions using a prospective longitudinal design is required.

#### **Introduction**

Previous research has shown that patients with chronic fatigue syndrome (CFS) present with an abnormal exercise response and exacerbation of symptoms after physical activity. Some of the main findings were a reduction in peak oxygen uptake,[2,10] reduction in peak heart rate,[10] earlier exhaustion,[10] and accelerated glycolysis with increased lactate production.[30] Contrary to these findings, others found that the aerobic capacity of CFS patients lies within the low normal range.[23] The highly heterogeneous nature of the CFS population and the lack of uniformity in both the utilized diagnostic criteria and exercise testing protocols preclude pooling of data and hence to draw firm conclusions. Still, we conclude that at least a subgroup of CFS patients present with an abnormal response to exercise. In addition, because several exercise capacity variables (e.g., functional aerobic impairment, body weight-adjusted peak oxygen uptake, exercise

duration) correlated with activity limitations/participation restrictions,[20] evidence supporting the clinical importance of impairments in exercise performance fitness in CFS patients was provided (i.e., a poor exercise performance was associated with more severe activity limitations/participation restrictions). Importantly, the exacerbation of symptoms after exercise is seen only in the CFS population, and not in fatigue-associated disorders such as depression, rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis.[26] To date, the exact cause of the abnormal exercise performance in CFS remains to be elucidated. Earlier attempts revealed that in CFS patients kinesiophobia (irrational fear of movement) is not related to exercise performance,[18] and that an exercise challenge further enhances complement activation.[26]

Type I interferons trigger the 2',5'-oligoadenylate (2-5A) synthetase/Ribonuclease (RNase) L activation and induce the expression of the double-stranded RNA dependent protein kinase R (PKR). The PKR enzyme and 2-5A synthetase/RNase L system are termed the cellular double-stranded RNA-detecting systems that are responsible for the translational inhibition in response to (viral) infection.[11] The deregulation of the 2-5A synthetase/RNase L pathway in subsets of CFS patients has been reported at length in the scientific literature.[3,27,28] Both elastases and calpain are capable of initiating high molecular weight RNase L (83 kDa) proteolysis, generating two major fragments with molecular masses of 37 (a truncated low molecular weight RNase L) and 30 kDa, respectively.[5] Experimental data point to an activation of the PKR enzyme, parallel to the 83 kDa RNase L proteolysis, in subsets of CFS.[8] PKR activation leads to phosphorylation of the inhibitor of NF(nuclear factor)-kB (I $\kappa$ B) and consequent NF-kB activation, which in turn causes inducible nitric oxide synthetase (iNOS) expression. iNOS generates increased production of NO by monocytes/macrophages. NO mediates important vital physiological functions such as neurotransmission, cell-mediated immune responses (strong antimicrobial and antitumour activities), and vasodilatation. Excessive and/or persistent production of NO, however, is detrimental to the body's functions.[21] Elevated NO has been documented in CFS patients.[14] Elevated NO levels and consequent vasodilatation might limit CFS patients to increase blood flow during exercise, and might even cause and enhance postexercise hypotension.[19] It is hypothesized that PKR activation and consequent elevated NO levels are related to poor exercise performance in CFS patients.

Snell and colleagues[25] showed that CFS patients with evidence of a deregulated 2',5'-oligoadenylate (2-5A) synthetase/RNase L pathway have a lower peak oxygen uptake than CFS patients without the intracellular immune deregulation, suggesting a link between immunopathology and exercise performance in CFS. As outlined previously,[19] the deregulation of the 2-5A synthetase/RNase L pathway may be related to a channelopathy, capable of initiating both intracellular hypomagnesaemia in skeletal muscles and transient hypoglycemia. This might explain muscle weakness and the reduced peak oxygen uptake seen in CFS patients. Thus, it is hypothesized that various components of the 2-5A synthetase/RNase L pathway (i.e., the ratio of 37 kDa RNase L to the 83 kDa native RNase L for the assessment of 83 kDa RNase L proteolysis, RNase L enzymatic activity, and elastase activity) are related to exercise performance in CFS patients. Summarizing the research questions, this study aims at 1) examining whether

PKR activation and consequent elevated NO levels predict poor exercise performance in CFS patients, and 2) examining whether exercise performance in CFS is associated with deregulation of the 2-5A synthetase/RNase L pathway (i.e., 83 kDa RNase L proteolysis, RNase L activity, and elastase activity). It is hypothesized that in CFS patients, 1) both PKR activation and consequent elevated NO levels predict poor exercise performance during a graded exercise cycle test, and 2) deregulation of the 2-5A synthetase/RNase L pathway is associated with poor exercise performance during a graded exercise cycle test.

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