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**POSTDOCTORAL FELLOWSHIP**  
(1) The original aims of the project  
The global objectives of this proposal were to assess the effects of aging and microgravity exposure on dynamic ventricular-arterial coupling, and to determine the optimal amount of physical activity to prevent deterioration of the ventricular-arterial coupling of the dynamic Starling mechanism. We proposed to test the following specific aims.  
1. To test the hypothesis that sedentary aging leads to progressive deterioration in dynamic ventricular-arterial coupling, we planned to examine a cross-section of sedentary individuals over decades (20-80 yrs old).
2. To test the hypothesis that life-long physical exercise training prevents the deterioration of the dynamic Starling mechanism with aging, we planned to recruit healthy individuals who have consistently trained at 2 different doses—the Surgeon General recommended goal of 150min/wk (Q3, 4-5 days/week) and a lower but possibly more realistic amount of 75-90 min (Q2, 2-3 days/week) for at least 25 yrs and compare these with sedentary elderly (Q1) and Masters athletes (Q4). 3. To test the hypotheses that prolonged exposure to microgravity in young healthy individuals promotes the deterioration of the dynamic Starling mechanism and that an optimized exercise training program can preserve the dynamic Starling mechanism even after prolonged exposure to microgravity, we planned to perform an exercise countermeasure during 5-week 6 degree head down bed rest. We planned to compare pre and post bed rest with and without the optimized exercise training.

(2) Key findings

The dynamic Starling mechanism represents the beat-to-beat modulation of stroke volume (SV) caused by beat-to-beat alterations in left ventricular filling, and reflects the complex interaction between ventricular and arterial stiffness. Spectral transfer function gain between beat-to-beat changes in SV and left ventricular end-diastolic pressure (LVEDP) was used as an index of the dynamic Starling mechanism. A right heart catheter was placed through an antecubital vein into the pulmonary artery. Beat-to-beat pulmonary artery diastolic pressure was used as an index of beat-to-beat LVEDP. Photoplethysmography was used to continuously measure finger arterial blood pressure. Beat-to-beat changes in SV were calculated from finger arterial pressure waveform with the Modelflow method. The main findings were as follows;

1. Sedentary aging leads to progressive deterioration in dynamic ventricular-arterial coupling: We have recruited a cross-section of sedentary individuals over decades (65: N=11, total 57 subjects). We found a linear relationship between the dynamic Starling mechanism index and their age (Index=-0.019xAge+1.71, R=0.594 P=0.002).

2. Life-long physical exercise training prevents the deterioration of dynamic Starling mechanism with aging: Effects of different levels of life-long exercise training on the dynamic Starling mechanism so far appear to be dose-dependent. The greater the amount of exercise training, the higher the indices of the dynamic Starling mechanism (Q1: 0.34±0.09, Q2: 0.50±0.24, Q3: 0.77±0.52, Q4: 0.97±0.54 ml/mmHg/m²).

3. 5-week head down tilt bed rest promotes the deterioration of the dynamic Starling mechanism: A total of 27 subjects underwent 5-week head down bed rest; 9 subjects without exercise countermeasure (sedentary group) and 18 subjects with exercise countermeasure (exercise group). Both sedentary (N=9) and exercise (N=18) groups showed a significant decrease of the dynamic Starling mechanism after the 5-week bed rest while the magnitude of the decrease in the dynamic Starling mechanism was significantly lower in the exercise group than in the sedentary group (Sedentary: -42%, Exercise: -12%, P=0.04). Based on the relationship between age and the dynamic Starling mechanism, the decrease in the dynamic Starling mechanism in the sedentary group was equivalent to 29 years of aging while that of exercise group was 9 years. These findings suggest that microgravity promotes the deterioration of the dynamic Starling mechanism with aging and that this deterioration can be partly prevented by exercise training.

(3) The impact of these findings on the hypotheses, objectives and specific aims:

1. The data until now support our hypothesis that sedentary aging leads to progressive deterioration in dynamic ventricular-arterial coupling.

2. The data until now support our hypothesis that life-long physical exercise training prevents the deterioration of the dynamic Starling mechanism with aging.

3. The data support our hypotheses that prolonged exposure to microgravity in young healthy individuals promotes the deterioration of the Starling mechanism with aging, and that an optimal exercise training strategy prevents, although it was partially, the deterioration of the dynamic Starling mechanism with 5-week head down bed rest.

Rationale for HRP Directed Research:

Congestive heart failure is the leading cause of hospitalization in the elderly (>65 years old), and its incidence and prevalence are increasing exponentially. Epidemiologic studies have shown that a large percentage (approximately 50%) of patients with congestive heart failure have a "preserved" ejection fraction (EF>40~50%) (CHF-pEF). Although studies addressing the pathophysiology of CHF-pEF are increasing in number with the recognition of the syndrome, its underlying mechanisms are still controversial. Although the mechanism of CHF-pEF has been a matter of vigorous debate, there are two major competing hypotheses that have been advanced to explain CHF-pEF. Both of these suggest static functional impairments in either left ventricular diastolic function or arterial compliance.

In this proposal, we proposed a novel index called the "dynamic Starling mechanism", the beat-to-beat relationship between LVEDP and SV at the respiratory frequency. The dynamic Starling mechanism is likely to unify ventricular-arterial compliance reflecting time-varying ventricular-arterial compliance. Furthermore, the Starling mechanism per se is generally accepted to be a key function pertaining to congestive heart failure. Our previous study showed that CHF-pEF patients have an impaired dynamic Starling mechanism compared with the sedentary elderly as age-matched controls. This finding suggests a novel explanation for the pathophysiology of CHF-pEF which has never been explained solely by ventricular diastolic function or by arterial stiffness.

Therefore, our finding that exposure to microgravity as well as sedentary aging leads to the deterioration of the dynamic Starling mechanism suggests that physical inactivity is a potential risk factor for the development of CHF-pEF. Moreover, our finding that exercise training prevents the deterioration of the dynamic Starling mechanism with aging and after exposure to microgravity implies that exercise training is a possible preventive strategy for the occurrence of CHF-pEF. As such, our findings will be beneficial for understanding the mechanism underlying cardiovascular diseases and may provide a possible preventive strategy.
1. To test the hypothesis that a sedentary aging leads to progressive deterioration in dynamic ventricular-arterial coupling, we planned to examine a cross-section of sedentary individuals over decades. To test the hypothesis that life-long physical exercise training prevents the deterioration of dynamic Starling mechanism with aging, we planned to recruit healthy individuals who had consistently trained at 2 different doses (N=10 per one group) - the Surgeon General recommended goal of 150 min/wk and a lower but possibly more realistic amount of 75-90 min for at least 25 yrs and compare these with the sedentary elderly and Masters athletes. We recruited 11 sedentary elderly, 5 elderly subjects with 75-90 min/wk, 7 elderly subjects with 150 min/wk, and 11 Masters athletes. The results so far support our hypothesis that life-long exercise training prevents the deterioration in dynamic Starling mechanism with aging, which is dose-dependent manner.

3. To test the hypotheses that prolonged exposure to microgravity in young healthy individuals leads the deterioration of the Starling mechanism and that an optimized exercise training program can preserve the dynamic Starling mechanism even after prolonged exposure to microgravity, we planned to perform an exercise countermeasure during 5-week 6 degree head down bed rest. We planned to compare pre and post bed rest with and without optimized exercise training (N=10 per group). Total 27 subjects have undergone 5-week head down bed rest, 9 subjects without exercise countermeasure (sedentary group) and 18 subjects with exercise countermeasure (exercise group). Both sedentary (N=9) and exercise (N=18) groups showed a significant decrease of the dynamic Starling mechanism after 5-week bed rest while the magnitude of the decrease in the dynamic Starling mechanism was significantly lower in the exercise group than in the sedentary group. These findings suggest that the microgravity promotes the deterioration of the dynamic Starling mechanism with aging and that this deterioration can be partly prevented by exercise training. We have completed the bed rest experiments although most of data still remain to be analyzed.

Bibliography Type:

**Abstracts for Journals and Proceedings**


**Articles in Other Journals or Periodicals**


