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 and a lower but possibly more realistic amount of 75-90 min for at least 25 yrs and compare these with the sedentary elderly.

3. To test the hypotheses that prolonged exposure to microgravity in young healthy individuals promotes 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.

(2) The key findings of the project

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 may reflect 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 (2). Life-long physical exercise training prevents the deterioration of dynamic Starling mechanism with aging: We recruited two elderly subjects so far (Age, 60 yrs old and 75 yrs old) who had been training at the level of Surgeon General recommended goal of 150min/wk for more than 25 yrs. From the relationship between the dynamic Starling mechanism index and age (Index=-0.022xAge+1.98), subjects with 60 yrs old and 75 yrs old are predicted to have the dynamic Starling mechanism index of 0.66 and 0.33, respectively. However, their dynamic Starling mechanism indices actually measured were 1.19 and 1.32, suggesting that life-long exercise training at the level of 150min/week prevents the deterioration in dynamic Starling mechanism with aging.

2. Life-long physical exercise training prevents the deterioration of the dynamic Starling mechanism: In sedentary aging, the dynamic Starling mechanism index of 0.42+/-0.16, exercise, pre: 1.15+/-0.47 post: 0.77+/-0.61). These findings suggest that microgravity promotes the deterioration of the dynamic Starling mechanism index and 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 supports 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. In addition, surprisingly, two subjects studied up to date, who had been training at the level of 150min/wk for more than 25 yrs, showed dynamic Starling equivalent to mechanism index than Masters athletes who had been training clearly more than these subjects (Group of 150min/wk; 1.25+/-0.09, Masters athletes; 0.96+/-0.55). This finding rather strengthens the hypothesis.

3. The data until now support our hypothesis that prolonged exposure to microgravity in young healthy individuals promotes the deterioration of the Starling mechanism with aging. At present it appears that our exercise training strategy may not completely prevent the deterioration of the dynamic Starling mechanism with 5-week head down bedrest. Final conclusions not only this point will be available after conclusion of the study.

(4) The proposed research plan for the coming year.

There have not been major problems for the subjects' recruitment, study protocol, and data analysis. Therefore, we plan to recruit 2 subjects for the group of 45-54 yrs old, 8 subjects for the group of 55-64 yrs old, 8 subjects for the group of 75 yrs old, and 7 subjects for the sedentary group of 5-week bedrest in the coming year.

Rationale for HRP Directed Research:

Congestive heart failure is the leading cause of the 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 propose a novel index called the "dynamic Starling mechanism" the beat-to-beat relationship between left ventricular end-diastolic pressure (LVEDP) and stroke volume (SV) at the respiratory frequency. Dynamic Starling mechanism is likely to unify ventricular-arterial compliance reflecting time-varying ventricular-arterial compliance, and further the Starling mechanism per se is generally accepted to be a key function pertaining to congestive heart failure. Our previous study shows that CHF-pEF patients have impaired dynamic Starling mechanism compared with the sedentary elderly as age-matched controls. This finding suggests a novel explanation for 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 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 implicates 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.

Task Progress:

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: 2. 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) at 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. We recruited two elderly subjects (Age, 60 yrs old and 75 yrs old) who had been training at the level of Surgeon General recommended goal of 150 min/wk for more than 25 years. The results support our hypothesis that life-long exercise training at the level of 150 min/wk prevents the deterioration in dynamic Starling mechanism with aging. We still need to recruit 8 subjects for the group of 150 min/wk and 10 subjects for the group of 75-90 min/wk.

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 14 subjects have undergone 5-week head down bedrest, 3 subjects without exercise countermeasure (sedentary group) and 11 subjects with exercise countermeasure (exercise group). Both sedentary (N=3) and exercise (N=11) groups showed a significant decrease of the dynamic Starling mechanism after 5-week bedrest while the magnitude of the decrease in the dynamic Starling mechanism was lower in the exercise group than 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 still have to recruit 7 subjects for the sedentary group to complete the project.

Bibliography Type: Description: (Last Updated: 09/06/2019)

Abstracts for Journals and Proceedings

Abstracts for Journals and Proceedings

Articles in Peer-reviewed Journals