Currently in clinical cardiovascular medicine, prospective randomized controlled trials are considered the “gold standard.” The larger, the better. Such studies are considered to have high internal validity. In recent years, such studies are often subsequently compared with “real-world” data from individual institutions and registries to augment their external validity. This approach has been the foundation for the enormous progress in understanding the pathobiology and treatment of cardiovascular disease during the past half-century. Colleagues in aerospace engineering and astronautics have made similar if not even more dramatic strides in the ability of humans to leave the earth, enter earth orbit, and go beyond. The demonstrated ability of humans to travel in space, walk on the moon, and remain in space for prolonged (months) time is nothing short of remarkable. The medium-term future likely entails even more prolonged space flight and travel to Mars. There has been considerable interest and productive work at the intersection of these 2 domains, namely, the evaluation and study of the effects of low or zero gravity on cardiovascular physiology and cardiovascular biology. Space flight produces dramatic changes in loading conditions, intravascular fluid status, and autonomic tone, all of which may be viewed as stressors, ultimately culminating in cardiovascular deconditioning. Once outside of Earth’s protective magnetosphere, astronauts have increased exposure to both solar and galactic ionizing radiation, which may result in adverse effects on the heart and vascular structures.

Given the dramatic innovations, fundamental knowledge, and future plans for the NASA program, there is the obvious need to determine the potential adverse effects of space flight on individual human beings. Indeed, we owe the brave astronauts who volunteer for this work nothing less. With the recent advent of commercial space tourism, one must additionally consider the potential cardiovascular consequences for civilians who have not passed through NASA’s rigorous astronaut selection process. Unfortunately, this is an area of clinical medicine and clinical investigation where large prospective randomized trials simply are not feasible. The number of astronauts, the rapid sequence change that characterizes the space program, and innumerable other factors all create the need to develop knowledge and evidence from approaches other than randomized trials.

It is from this perspective that the study of Charvat et al in this issue of Mayo Clinic Proceedings should be read and appreciated. In what is likely the largest and most comprehensive study of its kind, the authors retrospectively evaluated prospectively collected data on 303 American astronauts observed closely by the NASA program for Lifetime Surveillance of Astronaut Health. They evaluated the incidence of both hard (myocardial infarction, stroke, or cardiovascular death) and soft (percutaneous coronary intervention or coronary artery bypass grafting) cardiovascular events as well as mortality in this cohort. A conundrum is who should constitute the control group; who else has “The Right Stuff”? Wisely, they chose individuals from the Cooper Longitudinal Study (CCLS) to constitute a well-matched control group. Many studies often match participants and controls on a variety of baseline demographic (age, sex) and medical (comorbidities such as hypertension and diabetes) factors. What is novel about this study is the formation of the control group match for cardiorespiratory fitness as measured by formal exercise stress tests (bicycle and several standardized treadmill protocols). Cardiorespiratory fitness is an incredibly powerful control herein, as fitness likely serves as a mediator of cardiovascular health and mortality.
as well as a marker of innumerable unaccounted for comorbidities. Indeed, the average study participant was quite fit, able to achieve more than 13 metabolic equivalents of task, with mean values of maximal oxygen consumption of 46.6 and 46.3 mL/kg per minute for astronauts and CCLS participants, respectively.

The overall findings of the study were important. Regarding the primary outcome of cardiovascular deaths, the authors found no evidence of increased mortality risk in astronauts (hazard ratio, 1.10; 95% CI, 0.50 to 2.45). There was an increase in morbidity, specifically the combination of hard events (myocardial infarction, stroke, cardiovascular death) and all events (including revascularizations; hazard ratio, 2.41; 95% CI, 1.26 to 4.63). One obviously wonders if the sample size were larger or the follow-up longer whether the increase in nonfatal events would ultimately have an impact on mortality.

Certainly no one should expect space travel to be risk-free. Indeed, it is but one example of exploration (mountaineering or underwater study) or exposure to the unknown (medical research studies) where there is some risk to the participants. Quantification of that risk to better understand the mechanisms and ultimately provide mitigation are required, for both the individuals and society. This study by Charvat et al is one small step in that direction.

**POTENTIAL COMPETING INTERESTS**
The authors report no competing interests.

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