CARDIOPULMONARY DISCIPLINE SCIENCE PLAN

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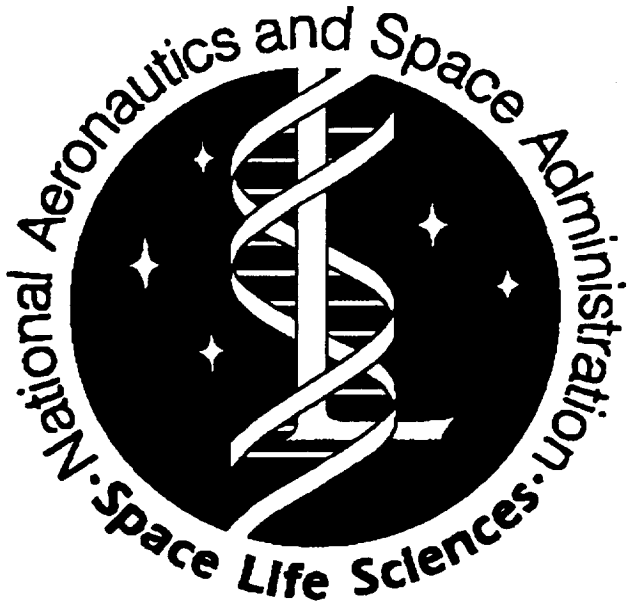

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CARDIOPULMONARY DISCIPLINE SCIENCE PLAN
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1.0 INTRODUCTION

As the U.S. Space Program prepares for extended-duration space flights on the Space Shuttle, on Space Station Freedom, and on exploration missions to the Moon and Mars, life sciences research must provide an understanding of the physiological changes that occur and develop effective countermeasures to any effects that may be detrimental to the functional capacity, health, or well-being of crewmembers. Life sciences research in the cardiopulmonary discipline must identify possible consequences of space flight on the cardiopulmonary system, understand the mechanisms of these effects, and develop effective and operationally practical countermeasures to protect crewmembers inflight and upon return to a gravitational environment.

The long-range goal of the NASA Cardiopulmonary Discipline Research Program is to foster research to better understand the acute and long-term cardiovascular and pulmonary adaptation to space and to develop physiological countermeasures to ensure crew health in space and on return to Earth.

1.1 PURPOSE

The purpose of this Discipline Science Plan is to provide a conceptual strategy for NASA's Life Sciences Division research and development activities in the comprehensive area of cardiopulmonary sciences. It covers the significant research areas critical to NASA's programmatic requirements for the Extended-Duration Orbiter, Space Station Freedom, and exploration mission science activities. These science activities include ground-based and flight; basic, applied, and operational; and animal and human research and development. This document summarizes the current status of the program, outlines available knowledge, establishes goals and objectives, identifies science priorities, and defines critical questions in the subdiscipline areas of both cardiovascular and pulmonary function. It contains a general plan that will be used by both NASA Headquarters Program Offices and the field centers to review and plan basic, applied, and operational (intramural and extramural) research and development activities in this area.

2.0 BACKGROUND AND CURRENT KNOWLEDGE

Current knowledge about physiological changes associated with short-term and long-term space flight is summarized in Appendix I, which is from Space Physiology and Medicine, 2nd. edition by Drs. Nicogossian, Leach-Huntoon, and Pool.

2.1 CARDIOVASCULAR PHYSIOLOGY

Concerns about cardiovascular adjustments to weightlessness actually preceded manned space flight. Fortunately, the dire predictions of circulatory failure and pulmonary edema proved incorrect, and there have been virtually no clinically overt adverse effects on the cardiovascular system during weightlessness. However, the readjustment to gravity following flight is associated with a number of cardiovascular

problems. Crewmembers returning from both short- and long-duration space flights undergo several changes in cardiovascular function, principally reduced orthostatic tolerance and decreased aerobic exercise capacity. Although these changes may pose a greater problem for future, longer duration flights, they are also a concern for the current short-duration Shuttle missions. It is estimated that many returning Shuttle crewmembers would have problems exiting the vehicle if an emergency egress were required immediately after landing. This problem has been worsened by the use of the bulky, heavy, partial-pressure Launch and Entry Suit (LES) now required for all post-Challenger flights.

Various mechanisms for cardiovascular adjustments in microgravity have been postulated: decreased intravascular volume, increased postflight venous pooling because of both structural and reflex vascular changes in the blood vessels of the splanchnic region and the lower extremities, and alterations in overall cardiovascular reflex control. In-flight orthostatic tolerance was determined during the Skylab missions by measuring heart rate and blood pressure during progressive levels of lower body negative pressure (LBNP). Decreased tolerance occurred within days after reaching orbit, and persisted, relatively unchanged, for the duration of the flight. Exercise capacity during the Skylab flights was relatively well-maintained, although maximal exercise capacity was not formally tested, and small decrements would not have been detected. Despite the apparent inflight preservation of aerobic exercise capacity, postflight capacity was significantly depressed. Substantial decreases in capacity were also reported by the Soviets in their flights of 1-12 months. The decrements were found even though postflight exercise testing has been performed in a supine position to reduce the effects of vascular volume deficit and of blood pooling. The time course of the recovery has not been well defined.

A variety of countermeasures has been instituted to counteract the cardiovascular changes associated with space flight. Aggressive in-flight exercise programs seem to be only partially effective. Soviet cosmonauts currently exercise daily during flight and use oral saline loading and anti-g suits to minimize orthostatic intolerance postflight. U.S. astronauts follow a similar program, although there is no formal requirement for exercise during flight and both exercise and fluid loading regimens vary according to crew preference. The Soviets also use daily LBNP with saline loading in the last 3 weeks of flight to improve orthostatic tolerance. According to their reports, some improvement in orthostatic tolerance occurs, but substantial disability remains, especially after flights of more than 2-3 weeks' duration.

Echocardiography has shown decreased chamber dimensions in crewmembers inflight when referenced to supine, Earth-based control values; but blood pressure, heart rate, and left ventricular volumes during flight are similar to those in upright subjects. Furthermore, Soviet scientists have reported microvascular changes in rats and monkeys flown in their COSMOS biosatellites for periods of up to 14 days. They also report venous congestion and vascular hyperplasia in a variety of tissues, including the heart, lungs, kidney, and meninges. These changes may be related to the cephalad fluid shifts, facial edema, and increases in renal size seen in long-duration human flights.

Arrhythmias have been reported in both U.S. and Soviet flights. Evidence from the Apollo Program and sporadic monitoring on Space Shuttle flights suggests a low incidence of arrhythmias during space flight. Increased plasma catecholamines

associated with psychological stress; heavy upper-body isometric exercise required to function in partial-pressure, soft-shell space suits; hypokalemia; hypercalcemia; thermal loads; and other cardiac changes have been suggested as etiological factors. But whether these factors have any arrhythmogenic role in space flight is unknown. Recently concluded agreements for monitoring of both Soviet cosmonauts and U.S. astronauts should provide additional information.

In addition to the obvious operational questions concerning cardiopulmonary physiology in microgravity, there are a number of other questions that can be studied best in microgravity. In the cardiovascular system, there appear to be changes in reflex regulation of circulatory function after flights of only a few days' duration. Carotid sinus response curves derived from heart rate changes associated with experimentally altered carotid artery transmural pressures suggest a decreased baroreflex responsiveness after flights of only 4-5 days' duration. Furthermore, the rapid response of the cardiovascular system to the cephalad fluid shifts in microgravity provides a unique opportunity to gain insight into several important cardiovascular regulatory mechanisms.

Limited information is available on the effects of space flights over 6 months on cardiovascular function.

2.2 PULMONARY PHYSIOLOGY

There have been no pulmonary problems associated with weightlessness *per se*, although there are problems and concerns associated with exposure to toxins and with operations in hypobaric or hyperoxic environments. Skylab studies showed only small changes in spirometry and no change in pulmonary function or gas exchange efficiency during submaximal exercise. The absence of clinical or operational problems in flight associated with primary changes in pulmonary function has meant that little research attention has been directed to this area. However, a recent German/Soviet report of a drop in PO_2 of arterialized capillary blood during long-term flight in Mir, and persistence of the hypoxemia for a brief period after landing, suggests that research is overdue. Furthermore, Soviet scientists have observed significant reductions *in* P_aO_2 in head-down-tilt experiments, suggesting P_aO_2 of crewmembers may be changed in microgravity. Lung function can be altered by changes in vascular pressures and volumes, and the lung can be damaged by inhaled gases, vapors, and aerosols. Integrity and normalcy of the pulmonary system cannot be assumed simply because of lack of symptoms or overt clinical signs. The absence of gravity also provides a model for examining the effect of gravity on blood flow and ventilation gradients on pulmonary function and cardiopulmonary interactions such as the nature and determinants of cardiogenic oscillations or the effects of lung compliance on ventricular filling and compliance. Some data related to ventilation-perfusion relationships and cardiogenic oscillations during space flight were obtained on the Spacelab Life Sciences - 1 mission and are currently being analyzed.

3.0 DISCIPLINE GOALS AND CRITICAL QUESTIONS

3.1 GOALS

The overall goals of the cardiopulmonary program are to:

- Understand the acute and long-term cardiovascular and pulmonary adaptation to space and readaptation to a gravity environment, including the associated mechanisms.

- Ensure adequate physiological countermeasures.

Specific questions related to cardiovascular and pulmonary physiology are listed below. Both human and animal models will be needed in studies designed to answer these questions. This plan incorporates recommendations from reports by the Committee on Space Biology and Medicine (Goldberg), the NASA Life Sciences Strategic Planning Study Committee (Robbins), and the Federation of American Societies for Experimental Biology (FASEB) (see 6.0, Selected References).

3.2 CRITICAL QUESTIONS

3.2.1 Cardiovascular (in priority order)

1. Of the various countermeasures available to combat adverse cardiovascular effects on long- and short-duration missions, which are most effective, when and how should they be applied, and in what sequence? These include but are not limited to LBNP, fluid rehydration, pharmacology, centrifugation, exercise and anti-g devices.

2. What are the nature, time course, and sequence of cardiovascular adjustments to space flight (acute, medium term, and long term)? Characterization of these adjustments should include assessment of hemodynamic, electrophysiological, neurohumoral, endocrine, histological, and molecular changes.

3. What are the specific mechanisms underlying the orthostatic hypotension observed after flight? What are the effective countermeasures for this?

4. What are the cardiovascular responses to extravehicular activity (EVA) at various levels of gravity (e.g., microgravity, planetary excursion)? What factors influence the occurrence, magnitude, and sequence of these responses?

5. What is the relationship between the cardiovascular adjustments to space flight and those occurring in Earth-based models such as bedrest, immersion, and head-down tilt?

6. Are the baroreflexes modified by space flight and how do these affect orthostatic tolerance? Are chemoreflexes and osmoreflexes modified by space flight and how do these affect orthostatic tolerance?

7. Is there an increase in cardiac arrhythmias associated with space flight and, if so, what is the time course of their occurrence and what are the specific mechanisms responsible for them?

8. What are the specific mechanisms underlying decreased aerobic capacity observed after flight? Are these changes present during flight? What are the effective countermeasures for this? What are the most effective exercise protocols for minimizing loss of aerobic capacity? Can exercise adequate for maintaining muscle and bone mass produce cardiovascular adaptations to sufficiently reduce the loss of aerobic capacity?

9. Do crewmembers become fully adapted to the weightless condition during space flight? And does the extent of adaptation affect postflight orthostatic tolerance?

10. How are countermeasures to adverse cardiovascular effects of long-duration space flight affected by changes in fluid distribution and metabolism?

11. Are there appropriate animal and/or computer models for studying each functional element of cardiovascular adjustments to microgravity?

12. Following long-term space flight, are there delayed or persistent consequences, either beneficial or harmful? As a corollary, are there appropriate rehabilitative measures that should be applied both in the near-term (hours to days) and long-term (months to years) after flight?

13. Since microgravity alters blood pressures and flows to some tissues, what are the structural and functional consequences in these various tissues and organ systems, including the myocardium, with long-duration flights?

14. Does space flight affect cardiovascular aging or disease processes commonly found in adults in a 1-g environment? How is subclinical cardiovascular pathology (e.g., small atrial defects, mitral valve prolapse, hypertension) affected by space flight? Do these same questions apply to healing processes in various organs?

15. What, if any, cardiovascular morphological changes are associated with acute or long-term exposure to space flight (e.g., effects of microgravity, radiation, or environmental hazards in the spacecraft)?

16. Does atrophy of smooth muscle in the leg vasculature occur during long-term space flight? How are vascular endothelial structure and function altered by such exposure and what are the consequences?

17. What is the nature of the interplay between hemodynamic and electrophysiological responses to space flight and how much of this is reflex mediated?

18. What are the correlations between the physiological responses demonstrated in the various microgravity study environments (e.g., KC-135, COSMOS, Research Animal Holding Facility [RAHF]) that are available?

19. What is the nature, time course, and individual variability of recovery following space flight? Is there a different sequence in the adaptive events during this period for different individuals and, if so, are they age or sex related? What, if any, are the cumulative effects of multiple mission exposures?

20. For the well-documented changes in calcium metabolism associated with space flight, what are the direct and indirect consequences for electrical, mechanical, and vascular events in the heart and for the vascular system?

21. What is the relationship between cardiovascular response and exposure to varying gravity levels (force, time)? Is there a threshold?

22. Are there appropriate controls for these microgravity studies and, if so, what are they?

23. What is the relationship of cardiovascular adjustments to those produced by microgravity in other systems and vice versa?

24. What is the nature of microgravity-associated changes in the autoregulatory mechanisms of capillaries, arterioles, venules, and lymphatics? What role do these changes play in the adaptation to microgravity and return to normal gravity?

25. What is the nature of space-flight-induced changes in the secretion or effect of vasoactive substances, and what is the effect of duration of exposure to microgravity?

26. Are there changes in cardiac performance and contractile efficiency during exposure to microgravity?

27. Does redistribution of blood volume and flow during space flight affect pH, PO_2, or PCO_2, or HCO_3 in tissues of any organs and vice versa?

28. Are there cellular and subcellular changes in cardiac function? Are there changes in myocardial contractile proteins? Is there a change in excitation-contraction coupling mechanisms induced by space flight?

3.2.2 Pulmonary
(in priority order)

1. What are the risks for bubble formation and clinical decompression sickness associated with various pre-EVA denitrogenation/decompression schedules?

2. In the environment of microgravity, does the absence of sedimentation cause deeper penetration by aerosol particles in the lung? In the spacecraft environment, what are the aerosol concentrations, particle

size profiles, and bacterial contaminations? Do these factors constitute a health hazard?

3. Which pulmonary life support procedures should be used for effective protection or resuscitation of crewmembers in the event of loss of pressure in the EVA suit or cabin?

4. How do the combined influences of exercise, oxygen breathing, and pulmonary microvascular gas emboli affect pulmonary function (including P_aO_2, P_aCO_2, pH, HCO_3, hemoglobin, and hematocrit) during and after EVA?

5. Does space flight affect pulmonary aging or disease processes commonly found in adults in a 1-g environment? How is subclinical pulmonary pathology (e.g., incipient bronchospasm, early emphysema) affected by space flight? Do these same questions apply to healing processes in the lung?

6. Is pulmonary function altered in long-duration space flight?

7. Are there appropriate animal and/or computer models for studying each functional element of pulmonary adjustments to microgravity?

8. What is the relationship, if any, between the pulmonary adjustments to space flight and those occurring in Earth-based models such as bedrest, immersion, and head-down tilt?

9. Is the inequality of ventilation and blood flow, and its effects on gas exchange, altered by exercise in microgravity?

10. Are there changes in respiratory muscle structure and function in space flight, and do such changes affect maximal oxygen uptake?

11. To what extent do lung volumes change in microgravity, and specifically how far does functional residual capacity decrease? Do these changes in lung volumes affect pulmonary gas exchange? Do additional lung volume changes occur during sleep in microgravity and thus affect gas exchange? What is the effect of functional residual capacity (FRC) reduction on tolerance to 100-percent oxygen breathing before and during EVA?

12. What changes occur in rib cage, diaphragm, and abdominal wall configurations during microgravity?

13. What happens to the gravity-determined topographical differences in blood flow, ventilation, alveolar size, intrapleural pressures, diffusion and mechanical stresses in microgravity, and how do these affect pulmonary gas exchange? Are there non-gravity-determined residual inequalities?

14. Does space flight affect central and/or peripheral respiratory control mechanisms? Are there factors in the space flight environment that

significantly influence the control of breathing? Are spacecraft CO_2 levels sufficiently low to preclude the development of acidosis, CO_2 retention and metabolic consequences, especially via renal and bone mechanisms?

15. Does space flight alter nonventilatory pulmonary function, e.g., immune, hormone, or enzyme mechanisms? Does this bear special relevance to the processing of and response to aerosolized antigenic stimuli?

16. If fluid transudation does occur, is this affected by exercise or other countermeasures, and is gas-exchange affected?

17. What is the combined effect of changes in lung volumes and alterations in mechanical stress and intrapleural pressure on the pericardial pressure in microgravity? What practical steps should be made to reference thoracic intravascular pressures to transvascular pressures?

18. To what extent are pulmonary vascular and microvascular pressures and interstitial fluid-lymphatic transport altered by microgravity? Are there any clinically significant consequences of these changes and what are they?

4.0 TECHNOLOGY

There are several technological requirements that are critically needed for conducting cardiopulmonary research in microgravity. Much of the hardware needed for human research is already available for laboratory or clinical use, but flight-qualified units should be developed. As a general principle, noninvasive monitoring devices are usually preferable. The need for flight equipment and facilities for animal research is even greater. Unavailability of cardiovascular sensors remains a key limiting factor, particularly for animal studies. The following is a table of critical technologies.

Table 1
WORKING LIST OF HARDWARE

CARDIOVASCULAR

1. Pressure transducers
   - a. Human
     - Improved automatic cuffs
     - Smaller, reliable, digital pressure
     - Beat-to-beat blood pressure, e.g., calibrated applanation tonometer
     - Improved central venous pressure
     - Device to measure vascular capacitance noninvasively
   - b. Animal
     - More reliable biosensors
     - Develop technology for external barometric reference for implantable transducer

Develop transducers for chronic implantation which would allow measurement of pleural and airway pressures
Technique for reliable long-term pericardial pressure recording
CSF transducer technology
Intracranial pressure transducer technology
Develop implantable telemetry units that could be used for changes in dimensions, temperatures, flows, pressures, etc.

2. Flow
   a. Human
      Improved accuracy for cardiac output determination
      1. Foreign gas/rebreathing
      2. Indicator dilution method
      3. Doppler
      4. Isotopes
      Develop/obtain techniques for regional flow determinations (e.g., laser Doppler, plethysmograph, NIR)
   b. Animal
      Improved flow transducer (Doppler or EMF)
      Method to record venous return accurately
      Coronary sinus flow recording

3. Dimensions/volumes
   a. Human
      Improved echo cardiac and vascular imaging technique
      Improved technique for body segment volumes
      Radionuclide technologies and other techniques for blood volumes
   b. Animal
      Implantable conductance technique (volume)
      Improved sonomicrometry techniques
      Radionuclide

4. Electrophysiology
   a. Human
      In-flight high-resolution, multi-lead ECG, with real-time processing/data compression
      Telemetry ECG
   b. Animals
      Electropotential transducer
      Improved radiotelemetry ECG
      Telemetry controllable pacing system

Improved LBNP device capable of sinusoidal pressures
Calibrated exercise devices

PULMONARY

Respiratory gas analysis
Blood gas analysis
Gravity-independent flow meters
Gas storage, mixing, and delivery system
Hemoglobin/oxygen saturation telemetry system
Aerosol production and delivery system

GENERIC

Devices to measure body mass, volume, and surface area in humans and animals
Device to measure and collect urine
Intravenous infusion kit, pump
Improved kits to collect, process, and store blood, including centrifuge, freezer,
trash capability
Glovebox workstation that allows handling of animals, specimens, toxic/hazardous materials (e.g., glutaraldehyde, isotopes, biohazards)
Freezers and refrigerators
Waste storage system for biohazards
Implantable chemosensors (e.g. for Ca^{++})
Method to handle and inject isotopes

4.1 ACCURATE MEASURE OF CARDIAC OUTPUT FOR BOTH HUMANS AND ANIMALS

Current methods for determining cardiac output include foreign gas rebreathing, echocardiography, Doppler ultrasound, and impedance cardiography for humans, and implantable Doppler and electromagnetic flow probes in animals. The most appropriate technique depends on the specific circumstances during the measurement. A remaining problem is the frequent operational instability of biosensors used in animal studies. Because of their greater accuracy at present, foreign gas rebreathing methods for determining cardiac output in humans should be implemented for all pre- and postflight testing. Because of current logistical constraints, less complicated methods are still required for in-flight monitoring.

4.2 ACCURATE MEASURE OF HEART RATE AND BLOOD PRESSURE

Several techniques permit measurement of beat-to-beat systemic arterial pressure. Records of ECG and beat-to-beat blood pressure could be analyzed for first order hemodynamics, variability, spectral content, power, etc., and correlated with other indices of cardiopulmonary function. Noninvasive blood pressure measurement systems recently adapted for flight use by the Johnson Space Center should provide accurate measurements, and these systems merit implementation.

Some investigations will require technology not presently available, which includes the need for calibrated, noninvasive, continuous recording of blood flow and pressure, radiotelemetry techniques, and a technique for pleural pressure recording.

Respiratory gas measurements are critical for most pulmonary function studies. Equipment such as light-weight, stable mass spectrometers and ultrasonic flow meters is complex, but should be obtained and modified for flight.

5.0 RESEARCH STRATEGY

The cardiopulmonary research area priorities for each of the NASA mission eras are presented in Table 2.

Table 2a
RANKINGS OF RESEARCH AREA PRIORITIES FOR EACH MISSION ERA

CARDIOVASCULAR	STS ERA CURRENT 1992-1995	SPACE STATION ERA 1991-2000	EXPLORATION ERA 2000-3000
Hemodynamic Mechanisms (Orthostatic Tolerance)	4.5	3.5	3
Orthostatic Tolerance Countermeasures	1	2	1.5
Electrophysiology (Arrhythmias)	2.5	3.5	6
Work Capacity (Exercise, Aerobic Training, EVA)	2.5	1	1.5
Integrated Studies	6	6.5	5
Validation of Models and Controls	4.5	5	7.5
Morphological & Microcirculatory	7	8	7.5
Cellular/Biochemical	9	9	9
Medical Issues	8	6.5	4

Table 2b

PULMONARY	STS ERA CURRENT 1992-1995	SPACE STATION ERA 1991-2000	EXPLORATION ERA 2000-3000
Pulmonary Function	4	5.5	4
Morphological & Microcirculatory	7	7	7
Long Deposition of Aerosols	2	2	1.5
EVA/Denitrogenation	1	1	1.5
Integrated Studies	5.5	5.5	6
Validation of Models and Controls	3	4	5
Medical Issues	5.5	3	3

The research plan incorporates a balanced program of both basic and applied efforts conducted in parallel. Although hypotheses concerning countermeasures against adverse cardiovascular effects have their foundation in ground-based physiology, space flight studies will serve to validate and refine Earth-based models. An integrated approach merging human and animal experimentation and computer modelling should be implemented. The basic science issue centers on understanding

short- and long-term cardiovascular adaptation to microgravity and readaptation to gravity conditions of 1-g or greater. The applied science concern focuses on the countermeasures needed to maximize crew health and safety and optimize performance. Countermeasures should be based on sound physiological principles and be testable by objective criteria and statistical approaches. To date, most of the in-flight investigations of cardiopulmonary function have tended to ask practical, operationally relevant questions. As the safety of crewmembers with regard to cardiovascular function for short-duration missions becomes apparent, the opportunity to address many of the cardiopulmonary questions from a more basic, mechanistic approach will increase. It is clear that many of these physiological questions can be answered only by taking a "systems" approach, although careful study and understanding of pressure and flow to the various organs will be an important component of such an overall approach.

An accessible data base is the first component needed to develop a comprehensive program in cardiopulmonary space physiology. Research from space medicine must be designed and conducted in a manner that will encourage publication in widely distributed, peer reviewed publications.

Orthostatic intolerance and diminished exercise capacity remain significant problems after flight. To approach this problem, a high priority must be given to systematic data collection, especially directed toward identifying specific predisposing cardiovascular changes and their underlying mechanisms. Blood pressure and heart rate are usually measured manually in both the U.S. and Soviet programs. A simple, single-channel ECG with beat-to-beat blood pressure monitoring would give important new information regarding the extent and time course of the readaptation process. High quality recording of the ECG would allow spectral analysis and correlation with changes in simultaneously measured blood pressure (vide infra). Those simple parameters, combined with cardiac output measurements (CO_2 or foreign gas rebreathing) and forearm skin blood flow determination, conducted supine and standing, would answer the question as to whether vasoconstriction and tachycardia occur appropriately, or if important reflex mechanisms are changed. Blood volume determination, coupled with measures of plasma catecholamines, would provide information regarding volume status and neurohumoral responsiveness. Current measures of carotid baroreflex sensitivity should be continued until sufficient numbers of subjects are obtained to permit analysis, but correlative data regarding cardiac output, stroke volume, and peripheral resistance must be obtained for a "system" level interpretation. Functions of the aortic baroreceptor reflexes should also be assessed. Further studies to quantify postflight venous pooling in the legs should be continued as well. Maximal exercise capacity should be assessed in conjunction with other cardiovascular and musculoskeletal testing. Such a coordinated approach is required to distinguish cardiovascular and skeletal muscle components of any observed deconditioning. A suitable protocol for this purpose could be conducted on an appropriate number of crewmembers in pre- and immediate postflight periods.

Associated ground-based studies must address the body's handling of saline and other fluid-loading interventions, as well as the effects of LBNP on intravascular volume retention, orthostatic intolerance, and upright exercise capacity. Additional studies must also examine whether changes in the microvasculature are responsible for alterations in fluid volume distribution, tissue pressure, and blood flow associated with cardiovascular adjustments to microgravity and return to Earth. There are virtually

no data on changes in vascular permeability, tone, structural integrity or endothelial function following exposure to microgravity, despite widespread clinical recognition of in-flight problems such as facial edema, persistently cold lower extremities, and a 10-15 percent decrease in calf volume, as well as lower extremity petechiae, which appear after completion of long-duration flights.

Arrhythmias have been a concern in both U.S. and Soviet crewmembers, yet there is limited information regarding the actual prevalence of arrhythmias in any phase of Shuttle flight other than during extravehicular activity (EVA). The frequency of arrhythmias in crewmembers should be determined before, during, and immediately after flight. Appropriate aeromedical assessment methods and interventions could then be developed on the basis of the data obtained.

It is possible that there are no ideal ground-based models for space-flight-induced cardiovascular changes. Currently used ground-based models include supine and 5- to 7-degree head-down bedrest, immersion, and lower body positive pressure. Soviet scientists have reported that "anti-orthostatic bedrest" (5-degree to 7-degree head-down tilt) is a satisfactory model of the changes associated with microgravity, but there is a need for additional flight data to substantiate this hypothesis. The Spacelab Life Sciences 1 (SLS-1) mission included head-down tilt studies on the flight crews, as does SLS-2. Head-down-tilt studies should be the same duration as the flights. These studies should provide a more direct assessment of the validity of the head-down-tilt model. These studies test some of the hypotheses regarding acute fluid shifts, but will not simulate the adjustments expected after extended-duration flights. If short-term data indicate validity of the hypothesis, a mission-length study postflight should be given high priority to provide a more rigorous test of the head-down tilt model.

Many questions relating to cardiovascular physiology may be addressed in man by noninvasive technologies. Other indices of performance of the cardiovascular system, however, require some information relating to pressure and flow as well as volume or dimension. In some cases, morphological or histochemical data are required. Because of ethical and engineering constraints, many of these data are not easily collected in humans and therefore require an animal model. Since baroreflex mechanisms are thought to be important for many of the in-flight and postflight changes observed in cardiovascular performance, it is important to choose an animal model with baroreflexes as similar to man as possible. For this reason, primates have a distinct advantage over quadripeds. Furthermore, certain primate species have cardiovascular hemodynamic properties that mimic those of humans. Chronically instrumented primates have been used for ground-based studies in aerospace cardiovascular research, and a limited degree of instrumentation has been performed on COSMOS biosatellites. A primate fully instrumented for multiple invasive cardiovascular variables has not been subjected to actual space-flight studies. Research should be conducted to further develop biosensors that are conducive to chronic instrumentation in animal models. More stability of transducers, improved biotelemetry systems, and new techniques of implantation, maintenance, and calibration may be required. Furthermore, animal models may be utilized to help validate Earth-based models of space-flight effects and computer models of cardiovascular function for these environments.

Clearer definitions and descriptions of potential applicability of animal experiments or computer simulations of the human space experience are needed. This applies to both cardiovascular and pulmonary changes. Opportunities on KC-135 parabolic flights and biosatellite flights as well as the primate RAHF and RHESUS programs for Spacelab, should be developed to examine cardiopulmonary changes in rats, as well as squirrel and rhesus monkeys. The findings from these experiments and the experience gained in developing flight hardware should be useful in planning research to be performed on future Spacelab flights and on Space Station Freedom, both in the pre-Permanently-Manned-Capability facilities and later in the Space Physiology Laboratory.

Countermeasures against microgravity-induced cardiovascular changes are currently being employed by both the U.S.S.R. and U.S. programs, but a strong physiological basis for these interventions is lacking. Both programs use fluid loading immediately prior to re-entry, but the optimal formulation of the composition of the solution, its amount, and the timing of administration are uncertain. Likewise, additional data are needed to support the extensive inflight use of lower body negative pressure. A similar need for physiological data exists with respect to the type and amount of inflight exercise needed. A systematic approach to the assessment of the various components of existing countermeasures and the development of new ones is badly needed.

The use of venous-occlusion thigh cuffs to mimic gravity-induced pooling of blood in the lower extremities has been mentioned by the Soviet scientists as an anti-orthostatic countermeasure. There are unsubstantiated reports that Soviet cosmonauts have worn occlusion cuffs during long-duration flights with excellent responses in terms of transient relief of facial edema, cephalad fluid shifts, and aerobic deconditioning. Such a countermeasure may be particularly well-suited for the short-term flights planned for the Space Shuttle over the next 2-3 years. As with the other "countermeasures," appropriate physiological measurements must be made to determine both the beneficial and possible harmful effects of this intervention.

The absence of gravity also provides a model for examining cardiopulmonary interactions, such as the nature and determinants of cardiac pulsatile action on small airway function.

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PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights[a] (1–14 days)	Long-Term Space Flights (more than 2 weeks)[b]	
		Pre- vs. Inflight	Pre- vs. Postflight
Cardiopulmonary System			
Heart rate (resting)	Slight increase inflight. Increased postflight; peaks during launch and reentry, normal or slightly increased during mission. RPB[c]: up to one week.	Normal or slightly increased.	Increased. RPB[c]: 3 weeks.
Blood pressure (resting)	Normal; decreased postflight.	Diastolic blood pressure reduced.	Decreased mean arterial pressure.
Orthostatic tolerance	Decreased after flights longer than 5 hours. Exaggerated cardiovascular responses to tilt test, stand test, and LBNP postflight. RPB[c]: 3–14 days.	Highly exaggerated cardiovascular responses to inflight LBNP (especially during first 2 weeks), sometimes resulting in presyncope. Last inflight test comparable to R + O[d] (recovery day) test.	Exaggerated cardiovascular responses to LBNP. RPB[c]: up to 3 weeks.
Cardiac size	Normal or slightly decreased cardio/thoracic ratio (C/T) postflight.		C/T ratio decreased postflight.
Stroke volume	Increased the first 24 hours inflight, then decreased by 15%.	Same as short duration missions.	12% decrease on average.
Left end diastolic volume	Same as stroke volume.	Same as short duration missions.	16% decrease on average.
Cardiac output	Unchanged.	Unchanged.	Variable RPB[c]: 3–4 weeks.
Central venous pressure (indirect measurement)	Gradual decrease over 7 days inflight.	Not measured.	Not measured.
Left cardiac muscle mass thickness	Unchanged.	Unchanged.	11% decrease, return to normal after 3 weeks.
Cardiac electrical activity (ECG/VCG)	Moderate rightward shift in QRS and T postflight.	Increased PR interval, QT_c interval, and QRS vector magnitude.	Slight increase in QRS duration and magnitude; increase in PR interval duration.
Arrhythmias	Usually premature atrial and ventricular beats (PABs, PVBs). Isolated cases of nodal tachycardia, ectopic beats, and supraventricular bigeminy inflight.	PVBs and occasional PABs; sinus or nodal arrhythmia at release of LBNP inflight.	Occasional unifocal PABs and PVBs.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights[a] (1–14 days)	Long-Term Space Flights (more than 2 weeks)[b]	
		Pre- vs. Inflight	Pre- vs. Postflight
Systolic time intervals	Not measured.	Not measured.	Increase in resting and LBNP-stressed PEP/ET Ratio. RPB[c]: 2 weeks.
Exercise capacity	No change or decreased postflight; increased HR for same O_2 consumption; no change in efficiency. RPB[c]: 3–8 days.	Submaximal exercise capacity unchanged.	Decreased postflight, recovery time inversely related to amount of inflight exercise, rather than mission duration.
Lung volume	Not measured.	Vital capacity decreased 10%.	No change.
Leg volume	Decreased up to 3% postflight. Inflight, leg volume decreases exponentially during first 24 hours, and plateaus within 3 to 5 days.	Same as short missions.	15% decrease in calf circumference.
Leg blood flow	Not measured.	Marked increase.	Normal or slightly increased.
Venous compliance in legs	Not measured.	Increased: continues to increase for 10 days or more; slow decrease later inflight.	Normal or slightly increased.
Body Fluids			
Total body water	3% decrease inflight.		Decreased postflight.
Plasma volume	Decreased postflight (except Gemini 7 and 8).		Markedly decreased postflight. RPB: 2 weeks increased at R + 0; decreased R + 2 (hydration effect).
Hematocrit	Slightly increased postflight.		
Hemoglobin	Normal or slightly increased postflight.	Increased first inflight sample; slowly declines later inflight.	Decreased postflight RPB: 1–2 months.
Red blood cell (RBC) mass	Decreased postflight; RPB: at least 2 weeks.	Decreased ~15% during first 2–3 weeks inflight; begins to recover after about 60 days; recovery of RBC mass is independent of the stay time in space.	Decreased postflight RPB: 2 weeks to 3 months following landing.
Red cell half-life (^{51}Cr)	No change.		No change.

Iron turnover			No change.
Mean corpuscular volume (MCV)	Increased postflight; RPB: at least 2 weeks.		Variable, but within normal limits.
Mean corpuscular hemoglobin (MCH)	Increased postflight; RPB: 2 weeks.		Variable, but within normal limits.
Mean corpuscular hemoglobin concentration (MCHC)	Increased postflight; RPB: at least 2 weeks.		Variable, but within normal limits.
Reticulocytes	Decreased postflight; RPB: 1 week.		Decreased postflight. In Skylab, RPB: 2–3 weeks for 28-day mission, 1 week for 59-day mission, and 1 day for 84-day mission.
White blood cells	Increased postflight, especially neutrophils; lymphocytes decreased; RPB: 1–2 days. No significant changes in the T/B lymphocyte ratios.		Increased, especially neutrophils; postflight reduction in number of T-cells and reduced T-cell function as measured by PHA* responsiveness; RPB: 3–7 days; transient postflight elevation in B-cells; RPB: 3 days.
Red blood cell morphology	No significant changes observed postflight.	Increase in percentage of echinocytes; decrease in discocytes.	Rapid reversal of inflight changes in distribution of red cell shapes; significantly increased potassium influx; RPB: 3 days.
Plasma proteins	Occasional postflight elevations in α2-Globulin, due to increases of haptoglobin, ceruloplasmin, and α2-Macroglobulin; elevated IgA and C_3 factor.		No significant changes.
Red cell enzymes	No consistent postflight changes.	Decrease in phosphofructokinase; no evidence of lipid peroxidation and red blood cell damage.	No consistent postflight changes.
Serum/plasma electrolytes	Decreased K and Mg postflight.	Decreased Na, Cl, and osmolality; slight increase in K and PO_4.	Postflight decreases in Na, K, Cl, Mg; increase in PO_4 and osmolality.
Serum/plasma hormones	Inflight increases in ADH, ANF, and decreases in ACTH, aldosterone and cortisol. Inflight decrease in glucose.	Increases in cortisol. Decreases in ACTH, insulin.	Postflight increases in angiotensin, aldosterone, thyroxine, TSH and GH; decrease in ACTH.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights[a] (1–14 days)	Long-Term Space Flights (more than 2 weeks)[b]	
		Pre- vs. Inflight	Pre- vs. Postflight
Serum / plasma metabolites & enzymes	Postflight increases in blood urea nitrogen, creatinine, and glucose; decreases in lactic acid dehydrogenase, creatinine phosphokinase, albumin, triglycerides, cholesterol, and uric acid.		Postflight decrease in cholesterol, uric acid.
Urine volume	Decreased postflight.	Decreased early inflight.	Decreased postflight.
Urine electrolytes	Postflight increases in Ca, creatinine, PO_4, and osmolality. Decreases in Na, K, Cl, Mg.	Increased osmolality, Na, K, Cl, Mg, Ca, PO_4. Decrease in uric acid excretion.	Increase in Ca excretion; initial postflight decreases in Na, K, Cl, Mg, PO_4, uric acid; Na and Cl excretion increased in 2nd and 3rd week postflight.
Urinary hormones	Inflight decreases in 17-OH-corticosteroids, increase in aldosterone; postflight increases in cortisol, aldosterone, ADH, and pregnanediol; decreases in epinephrine, 17-OH-corticosteroids, androsterone, and etiocholanolone.	Inflight increases in cortisol, aldosterone, and total 17-ketosteroids; decrease in ADH.	Increase in cortisol, aldosterone, norepinephrine; decrease in total 17-OH-corticosteroids, ADH.
Urinary amino acids	Postflight increases in taurine and β-alanine; decreases in glycine, alanine, and tyrosine.	Increased inflight.	Increased postflight.
Sensory Systems			
Audition	No change in thresholds postflight.		No change in thresholds postflight.
Gustation & olfaction	Subjective and varied human experience. No impairments noted.	Same as shorter missions.	Same as shorter missions.
Somatosensory	Subjective and varied human experience. No impairments noted.	Subjective experiences (e.g., tingling of feet).	

Vision	Transitory postflight decrease in intraocular tension; postflight decreases in visual field; constriction of blood vessels in retina observed postflight; dark adapted crews reported light flashes with eyes open or closed; possible postflight changes in color vision. Decrease in visual motor task performance and contrast discrimination. No change in inflight contrast discrimination, or distant and near visual acuity.	Light flashes reported by dark adapted subjects frequency related to latitude (highest in South Atlantic Anomaly, lowest over poles).	No significant changes except for transient decreases in intraocular pressures.
Vestibular system	40–50% of astronauts / cosmonauts exhibit inflight neurovestibular effects including immediate reflex motor responses (postural illusions, sensations of tumbling or rotation, nystagmus, dizziness, vertigo) and space motion sickness (pallor, cold sweating, nausea, vomiting). Motion sickness symptoms appear early inflight, and subside or disappear in 2–7 days. Postflight difficulties in postural equilibrium with eyes closed, or other vestibular disturbances.	Inflight vestibular disturbances are same as for shorter missions; markedly decreased susceptibility to provocative motion stimuli (cross-coupled angular acceleration) after 2–7 days adaptation period. Cosmonauts have reported occasional reappearance of illusions during long-duration missions.	Immunity to provocative motion continues for several days postflight. Marked postflight disturbances in postural equilibrium with eyes closed. Some cosmonauts exhibited additional vestibular disturbances postflight, including dizziness, nausea, and vomiting.
Musculoskeletal system			
Height	Slight increase during first week inflight (~1.3 cm). RPB: 1 day.	Increased during first 2 weeks inflight (maximum 3–6 cm); stabilizes thereafter.	Height returns to normal on R + 0.
Mass	Postflight weight losses, average about 3.4%; about 2/3 of the loss is due to water loss, the remainder due to loss of lean body mass and fat.	Inflight weight losses average 3–4% during first 5 days; thereafter, weight gradually declines for the remainder of the mission. Early inflight losses are probably mainly due to loss of fluids; later losses are metabolic.	Rapid weight gain during first 5 days postflight, mainly due to replenishment of fluids. Slower weight gain from R + 5** to R + 2 or 3 weeks. Amount of postflight weight loss is inversely related to inflight caloric intake.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights[a] (1–14 days)	Long-Term Space Flights (more than 2 weeks)[b]	
		Pre- vs. Inflight	Pre- vs. Postflight
Body composition		Fat is probably replacing muscle tissue. Muscle mass, depending on exercise regimens, is partially preserved.	
Total body volume	Decreased postflight.	Center of mass shifts headward.	Decreased postflight.
Limb volume	Inflight leg volume decreases exponentially during first mission day; thereafter, rate of decrease declines until reaching a plateau within 3–5 days. Postflight decrements in leg volume up to 3%; rapid increase immediately postflight, followed by slower RPB.	Early inflight period same as short missions. Leg volume may continue to decrease slightly throughout mission. Arm volume decreases slightly.	Rapid increase in leg volume immediately postflight, followed by slower RPB.
Muscle strength	Decreased inflight and postflight; RPB: 1–2 weeks.		Postflight decrease in leg muscle strength, particularly extensors. Increased use of inflight exercise appears to reduce postflight strength losses, regardless of mission duration. Arm strength is normal or slightly decreased postflight.
EMG analysis	Postflight EMGs from gastrocnemius suggest increased susceptibility to fatigue and reduced muscular efficiency. EMGs from arm muscles show no change.		Postflight EMGs from gastrocnemius show shift to higher frequencies, suggesting deterioration of muscle tissue; EMGs indicate increased susceptibility to fatigue. RPB: about 4 days.
Reflexes (Achilles tendon)	Reflex duration decreased postflight.		Reflex duration decreased postflight (by 30% or more). Reflex magnitude increased. Compensatory increase in reflex duration about 2 weeks postflight; RPB: about 1 month.

Nitrogen & phosphorus balance		Negative balances early inflight; less negative or slightly positive balances later inflight.	Rapid return to markedly positive balances postflight.
Bone density	Os calcis density decreased postflight. Radius and ulna show variable changes, depending upon method used to measure density.		Os calcis density decreased postflight; amount of loss is correlated with mission duration. Little or no loss from non-weightbearing bones. RPB is gradual; recovery time is about the same as mission duration.
Calcium balance	Increasing negative calcium balance inflight.	Excretion of Ca in urine increases during 1st month inflight, then plateaus. Fecal Ca excretion declines until day 10, then increases continually throughout flight. Ca balance is positive preflight, becoming increasingly negative throughout flight.	Urine Ca content drops below preflight baselines by day 10; fecal Ca content declines, but does not reach preflight baseline by day 20. Markedly negative Ca balance postflight, becoming much less negative by day 10. Ca balance still slightly negative on day 20. RPB: at least several weeks.

[a] Compiled from biomedical data collected during the following space programs: Mercury, Gemini, Apollo, ASTP, Vostok, Voskhod, Soyuz and Shuttle Spacelab.
[b] Compiled from biomedical data collected during Skylab and Salyut missions.
[c] RPB: Return to preflight baseline.