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Chapter

Preparation, Implementation and Execution of Human Cardiovascular Experiments in Space

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Abstract

There are eight steps in the preparation, implementation and execution of a human spaceflight experiment: (1) writing a proposal, (2) being selected by a space agency, (3) finding funding, (4) flight feasibility assessment for flight, (5) implementation into a specific space platform (e.g. the Space Shuttle in the past and now the International Space Station), (6) experiment execution, (7) analysis of collected data and (8) publication. The unique features about spaceflight experiments are steps 4–6 because of the limitations of conducting experimental procedures in space. Furthermore, all of the associated equipment have to be developed and approved for spaceflight with all the safety aspects taken appropriately into consideration. In this chapter, two specific experiments from the Spacelab D2 mission in 1993 are used as illustration of these steps as well as describing the use of parabolic flights as a preparatory platform. It is important to have data collected of such a quality that they can be published in science journals with external peer review. It is also important that the data not only have operational spaceflight applications but also can advance knowledge for terrestrial science purposes.

Keywords: cardiac output, cardiovascular, central venous pressure, parabolic flight, weightlessness

1. Introduction

On 22 March 1993, I was closely watching the big screen in the German Space Control Centre in Oberpfaffenhofen near Munich, Germany. The Space Shuttle with the Spacelab D2 mission was just about to lift off, and on board were seven astronauts and equipment for a host of experiments of which four were from Denmark. I was the responsible investigator for these four experiments. I was nervous. In the airplane from Copenhagen to Munich the day before, I had told myself that this would either be my stepping stone to a further career in space physiology and medicine or simply my big Waterloo. The Danish government had payed millions of Kroners in preparation of the studies, and failure was not an option. The problem, though, was that anything random, which was totally out of my and my colleagues' control, could happen at any time and jeopardise our experiments.

The four experiments had been under preparation for some 5 years and supported by Danish space research grants. Eight people had been full time involved in my laboratory: four engineers and four medical doctors. Equipment had been developed, tested and adapted for spaceflight, and many nervous moments had been overcome. It was exciting times and now—finally—everything was about to be launched into space to orbit the Earth at a speed of 28,000 km per hour in a free fall condition inducing chronic weightlessness for 10 days. I felt tense as the launch countdown approached zero.

A few seconds before launch, two of the three Space Shuttle engines ignited. The third one did not. Immediately we knew in the control room that something was wrong. One of the engines did not blast, and within a few seconds, all engines stopped. As water vapour evaporated away from the shuttle, we waited anxiously. What would happen now?

The ignition had failed, and within the next hour or so, the astronauts were let out, and the launch postponed until the end of April. In that interim period, we had to repeat some ground tests on the astronauts in collaboration with several other international teams from Europe and the United States. Finally, after some additional postponements of the launch, the Space Shuttle Columbia ignited on 26 April and went to space, where it completed a 10-day mission with great success. Almost 90 experiments were expertly conducted. Concerning the four Danish human physiology experiments, the data were successfully collected, which 2–3 years later led to three scientific papers [1–3] from our Danish space medicine and physiology laboratory, DAMEC Research Inc. (Danish Aerospace Medical Centre of Research Inc.), at the Copenhagen University Hospital.

The successful completion of our experiments on the Spacelab D2 mission in 1993 with the publications in 1995 and 1996 led to the later expert preparation, implementation and conduction of seven additional studies in space on the Russian Mir station, Space Shuttle Columbia and International Space Station. All studies had cardiovascular adaptation aspects, and parabolic flights were used—not only for preparation of the spaceflight experiments but also to obtain basic science knowledge of human physiological responses to very acute weightlessness of 20 s.

2. Experimental science background

During changes in posture, blood pressure in humans is continuously and acutely regulated by pressure reflexes originating from receptors (baroreceptors) in the aorta close to the heart and in the two carotid (neck) arteries at the base of the skull. In addition, there are pressure sensors in the heart, from which reflexes also originate to participate in blood pressure control. This blood pressure regulation is for the central nervous system to make sure that the perfusion pressures to the brain and other organs are optimal despite the displacement of blood caused by the posture. As an example, the upright posture displaces blood downwards towards the lower body and the legs away from the head and heart. To counteract that so that the blood pressure at heart and head level does not fall too much, which would impede blood supply to the brain, the blood pressure reflexes sense the decrease in pressure and within a few heart beats initiate an increase in heart rate and constriction of the small arteries in the lower body. The opposite occurs, when the posture changes from upright to recumbent or supine.

We have for many years investigated, which blood pressure sensors are the most important for adjusting blood pressure to posture changes. In a whole host of investigations using a combination of various models as well as short-term weightlessness during parabolic flights, we have aimed at isolating the effects of some

receptors versus others and found that in order for blood pressure and heart rate to adapt to either the supine or upright posture, the low pressure reflexes originating from the heart and major central veins are pivotal. Without the inputs from these low pressure heart and venous reflexes, the new steady state cannot be achieved. These findings have changed our previous understanding of how the human cardiovascular system adapts to changes in postures and the effects of gravity.

Since blood pressure is also determined by the amount of fluid in the body, we have used the human head-out water immersion model to investigate how the volume of fluid and amount of salt is controlled. By immersing humans in the seated posture to the level of the neck for hours, the fluid- and salt-excreting mechanisms through the kidneys are stimulated, because the headward shift of blood and fluid from the lower body to the heart through various mechanisms informs the central nervous system that the upper body vessels are being overloaded with blood and fluid so that this excess volume must be excreted. The mechanisms for this are still only partly understood, but the main opinion is that there is a connection between the heart and kidneys through what is termed the cardio-renal link so that when the heart chambers are stretched, it initiates a reflex response to the kidneys to excrete more salt and fluid in the urine.

Our research using the seated head-out water immersion model has shown that not only the cardio-renal link and associated hormones control the urinary excretion rates of sodium during shifting of blood and fluid to the upper body but also dilution of the blood with fluid from the tissues plays an important role. During shift of blood from the lower to the upper body caused by the surrounding water pressure, fluid is pushed into the circulation from the lower body tissues. This dilution can affect the kidneys directly as well as release of some kidney-regulating hormones.

Weightlessness in space is a unique condition that cannot be replicated on the ground and where bodily functions can be studied without the intervening effects of gravity. In space, blood and fluids are chronically displaced towards the upper body segments (heart and head), and the daily fluctuations induced by posture changes do not occur. This gives us a unique opportunity to utilise weightlessness in space for exploring the cardiovascular and fluid volume-regulating systems in the human body.

3. Experiments: the spacelab D2 mission in 1993

The experiments on the Spacelab D2 mission in 1993 aimed at understanding whether the blood and fluid shift into the heart during prolonged weightlessness would augment the urinary output of water and salt, just as we usually observe in ground-based simulation models. In one experiment we aimed at measuring how much the fluid pressure leading into the heart (central venous pressure, CVP) increases, which we at that time thought to be the stimulus for control of the urinary fluid and salt excretion. In another experiment we aimed at monitoring the urine production. It was the hypothesis that an increase in CVP induced by weightlessness would augment the excretion rate of fluid and salt.

3.1 CVP experiment

The CVP experiment was originally planned to be done on two of the Spacelab D2 astronauts, but for some technical reasons, it was only accomplished in one. The experimental plan was to shortly before launch insert a long catheter with a pressure transducer at the end into the vein directly leading into the right atrial chamber of the heart through a peripheral arm vein and connect it to a preamplifier

and a recording system. The test astronaut would thus be inserted with the catheter and wear the CVP monitoring system until 3 hours into the mission following launch. Thereafter the catheter would be withdrawn. Before the launch of the Space Shuttle, control measurements in different body postures were performed.

The equipment used for measurements of central venous pressure during the Spacelab D2 mission in one astronaut is depicted in **Figure 1**. The central venous catheter (1) with a pressure transducer placed at one end and a connector box at the other was plugged into a preamplifier (2) that was connected to a recording unit (3). A calibration piston (4) could be connected to the reference opening of the catheter and thus induce predetermined pressure changes on the backside of the transducer membrane. In this way, it was tested to what degree the calibration characteristics of the pressure transducer might have changed over time after being inserted into the astronaut. Following the spaceflight, the catheter was brought back to the investigators and tested for change in drift of the tip transducer.

3.2 Urinary excretion experiment

Before the spaceflight, four test astronauts would, over a 4.5-h period, empty their urine bladders in either supine or seated posture, on an hourly basis after being infused through a peripheral vein with isotonic saline in an amount of 2% of their body weight. About a week into the flight, the same would be done following a similar infusion while they thus would be free floating in the space vehicle. Blood was sampled on ground and during flight for determination of water-, salt- and blood pressure-regulating hormones. The volume of urine was measured after each void and samples taken for determination of salt (sodium and potassium) concentrations. In space, the volume of urine was determined by a urine monitoring system delivered by NASA, which was connected to the toilet. If the voids were felt by the subjects to be small, the bladders were emptied into bags and returned to

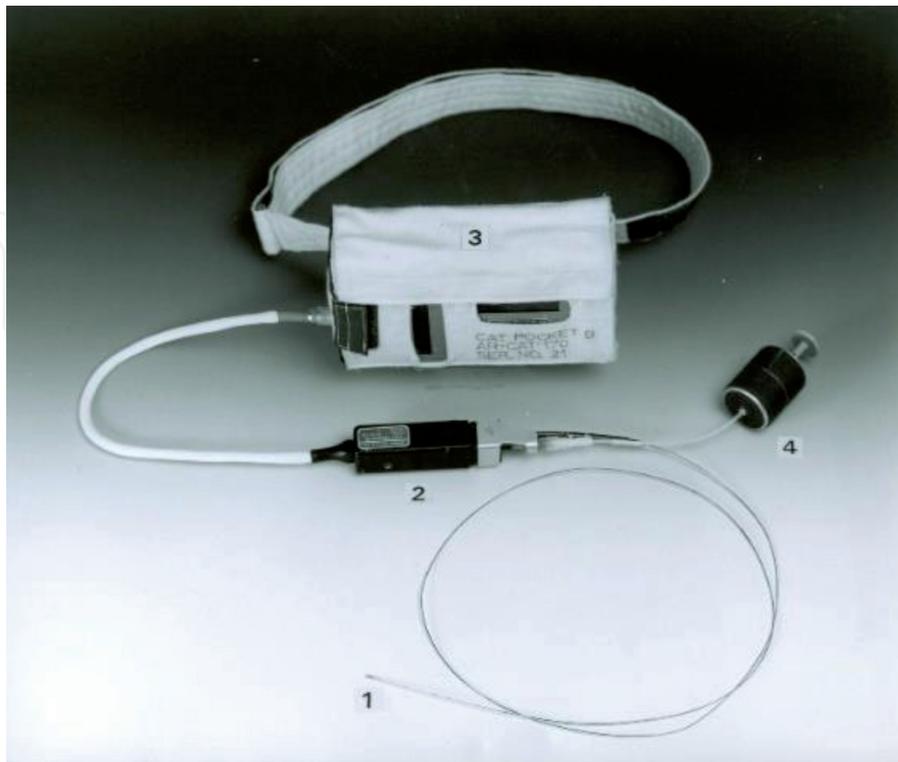


Figure 1. Central venous pressure equipment, which flew on the Spacelab D2 mission in 1993 [3]. (See text for detailed explanation).

Earth through the trash system on the Shuttle. The saline infusion was conducted over some 20 min by manually inflating a cuff-pressure system, and the amount varied on an average between 1.7 and 1.8 litres.

4. Experiments during subsequent missions (1995–2012)

After the Spacelab D2 mission in 1993, our research team in Denmark conducted additional experiments on various space platforms with one on the Russian space station, Mir, in 1995, where we monitored urine excretion rates over longer flight periods of up to 6 months by having three test astronauts collect urine into bags and the volumes measured by a scale system. The idea was to test whether urine production in weightlessness after intake of an oral water load would be enhanced—just like we tested the same hypothesis regarding urinary salt excretion on the previous Spacelab D2 mission.

During later space missions, we have conducted several additional studies on the Space Shuttle and the International Space Station focusing on the cardiovascular adaptation to short (<30 days) and long (>30 days) duration flights. In particular, we have for this purpose conducted cardiac output measurements by a non-invasive rebreathing technique, which has been developed for spaceflight. Cardiac output is the amount of blood injected by the heart into the body per minute, and this variable is important for understanding the effects of weightlessness on not only cardiac function but also the vascular condition in general. The hypothesis was tested that the weightlessness-induced increase in central blood volume would increase cardiac output and at the same time through the cardiovascular reflexes dilate the arterial resistance vessels to counteract an increase in blood pressure.

Normally, accurate cardiac output estimations require insertion of catheters into the veins and arteries, which makes the measurement difficult on a routine basis in normal healthy humans. With the non-invasive foreign gas rebreathing technique developed for spaceflight, such estimations can be done anytime and anywhere with no harm to the test subject. As indicated in **Figure 2**, the tested person breathes

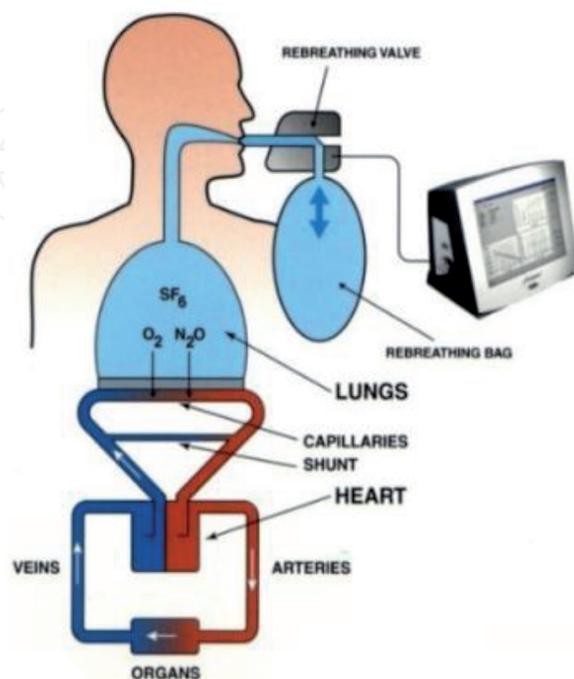


Figure 2.
The principle of foreign gas rebreathing for measurement of cardiac output [4]. (See text for explanation).

back and forth into a rebreathing bag with a gas mixture, in which a tracer gas (e.g. N_2O) is taken up by the blood flowing through the lungs. The disappearance rate of the tracer gas from the lungs to blood is detected by an infrared photoacoustic gas analyser connected to the mouthpiece of the rebreathing person. By knowing the solubility of the gas in the blood, the amount of blood flowing through the lungs per unit of time can be calculated. This amount is equal to cardiac output. The measurements take less than 30 s and are pivotal for understanding how cardiac output adapts to various conditions such as weightlessness in space [4].

This methodology is currently being used on the International Space Station for various research projects and has been developed from a mass spectrometry detection technique for measuring gas concentrations to using infrared photoacoustic gas detection. This has made it possible to have a much less voluminous and more user-friendly equipment on board the space station. Also, this technique has been tested against golden standard invasive clinical techniques, where excellent correlations have been found [5].

5. Microgravity experiment implementation and execution

The cardiovascular experiments that we have conducted in space through the past three decades entail the following steps: (1) proposal, (2) selection, (3) funding, (4) feasibility assessment, (5) implementation, (6) execution, (7) data analysis and (8) publication. The unique features about spaceflight experiments are steps 4–6, because of the limitations of conducting experimental procedures in space. Furthermore, all of the associated equipment have to be developed and approved for spaceflight with all the safety aspects taken appropriately into consideration.

5.1 Proposal

The first step for performing experiments in space is to develop a proposal and respond to a space agency solicitation from, e.g. the European Space Agency (ESA) or National Aeronautics and Space Administration (NASA). ESA's topics are usually broader than NASA's, because the latter are mostly focused on operational aspects. In both cases the proposal formats are rather similar and the subsequent selection process very much like the way it is done at the national levels with peer review panels and scientific merit scorings. In order for a proposal to be successful, the following criteria must generally be fulfilled:

1. Qualified research team with experimental experience from a university or a recognised company. Most proposals are from universities, and experience in space research is an advantage but not a requirement.
2. Clearly written proposal, which fulfils the requirements stated in the call.
3. Adherence to all of the rules and instructions—otherwise the proposals will be rejected upon receipt, and this includes adhering to the stated deadlines for submission.
4. Relevancy for utilising spaceflight meaning that what is proposed to be measured should be responsive to the flight environment (e.g. weightlessness).

One thing to keep in mind when writing a proposal is to formulate it so that non-experts in the field can also get something meaningful out of it, because at the

time of selection and thereafter, decision-makers who may not be scientists might make a judgement as to the appropriateness of spending resources in space for this particular experiment.

5.2 Selection

When a proposal is submitted in response to a research announcement, the first step is that it will be evaluated by scientists appointed by the space agency or a group of space agencies. The scientists—or peer reviewers—are usually experts within the field of the topic of the solicitation, who are not involved in collaborations with the proposers. The peer review panels are usually led by an agency representative, and the panel will score each proposal on a scale between zero and 100. Scores between 90 and 100 are categorised as “Excellent” or “Outstanding”, 80 and 89 as “Very Good”, 70 and 79 as “Good”, 50 and 69 as “Fair” and below 50 as “Poor”. The score threshold for selection may vary between space agencies, but usually no proposals are selected with a score lower than 70.

The next step for the space agency representatives is to—based on the peer review scores—perform final selections. In this case, not only the scientific merit scores play a role but also the relevancy of the proposal for the agency. Usually a subset of the highest scientifically scoring proposals are selected, but sometimes even proposals with the highest scores may not be finally selected because of less relevancy for the operational purposes of the agency. In this regard, there are different policies between the space agencies. For NASA, deep space explorations are the main drivers, while ESA usually focuses almost entirely on the scientific merit and the proposal’s ability to produce new fundamental knowledge to the scientific community.

5.3 Funding

In order for a selected proposal to be executed in space, funding has to be obtained. This can either be done by grants from local and national authorities or from the space agency itself. The problem in particular for European researchers is that for ESA to consider selection of a proposal, it is advantageous to have obtained national funding or a declaration of intention of funding already before submission. In many cases, national authorities will only indicate intention of funding, should the proposal be selected, but they usually will not guarantee it. This can sometimes create a hen and an egg problem: The space agency will—before it actually finally selects a proposal—require guaranteed funding from a national authority, whereas the national authority requires that the agency selects the proposal. The proposers usually obtain intention for funding in letters from the national funding authorities, and usually the space agency will accept that. In our case, when the research team was supported for selected experiments, we referred to an existing grant that could overlap with selection of a new proposal.

Funding of a grant for experiments in space usually only covers the expenses incurred by the experimental research team. The space infrastructure, such as access to a space vehicle and its astronauts (e.g. the Space Shuttle), is delivered by the space agencies.

5.4 Feasibility

When selection and funding are obtained, the space agency will conduct a feasibility study to evaluate whether the experiment can be implemented in space and whether there are technical or other obstacles. If these cannot be overcome,

the proposal will be de-selected. Usually the experiment is modified, if obstacles are detected. An obstacle for implementation may not just be technical such as lack of availability of a technique or equipment but may also be lack of astronaut crew time for execution of the experiment. In that case, the experiment is usually modified in close collaboration with the research team. If the experiment changes considerably, the space agency may require an additional scientific peer review to evaluate whether the scientific quality is still high enough, but this is not the usual process.

5.5 Implementation

When the space agency feasibility assessment has been successfully completed, meaning that the experiment can be conducted in space, the implementation process begins. All of our previous research team's selected experiments (10 in total) have been somehow modified during the feasibility assessment and implementation processes. The renal experiment on the Spacelab D2 mission in 1993 was changed by decreasing the number of inflight sessions from two to one, because of limited crew time. The purpose was as previously described to evaluate the effects of applying an intravenous saline fluid load to the test astronauts on renal excretion rates of fluid and sodium. We had originally planned a session with infusion and a session without, but only the infusion session could be implemented in space. Otherwise the experiment was kept intact except that it was actually improved by changing our proposed saline loading from an oral saltwater load to intravenous infusion. This was done because an experimental complement was created for the space mission, whereby several experiments were to be executed in an integrated fashion, and a US experiment had suggested to use saline loading by infusion. Thus, this intravenous infusion of isotonic saline was planned to be done for the first time ever in space.

Although the urinary experiment was not difficult to implement from a technical point of view, it was totally different regarding the CVP experiment. After selection of this experiment, many managers within ESA and NASA thought it would be impossible to be allowed to conduct such an invasive study. We succeeded anyway, which was because of one important thing: the backing of the appointed payload commander. Without this support for the experiment, it would never have been executed. The reason for the astronaut support was because of thrust in our research group's ability to conduct the study, which we obtained by always being well prepared for pre-flight briefings of the astronauts as well as for the pre-flight control studies. We always made sure that as much of the data that had been collected were properly analysed between the different ground tests and that the data were presented to the astronauts during the subsequent tests so that they together with the investigators could follow the progress of the study throughout the pre-flight period.

5.6 Execution

During the Spacelab D2 mission, I was standing in the mission control centre in Oberpfaffenhofen near Munich in Germany holding my breath and watching the big screen. All investigators followed the executions of their experiments from the mission control centre, and just before initiation of our renal experiment, which as described earlier was integrated into one complement, a valve was stuck in some of the equipment. If the valve problem was not solved, we would all risk that none of the experiments in the complement would be conducted. It was a tense moment, when the payload commander after directions from mission control finally got the valve to work and initiated the flow of measurements. What a relief!

During execution of our urinary excretion experiment a mistake did happen, whereby urine bags, which were to be collected after flight directly from the trash can in the Space Shuttle, were not correctly labelled. It meant that we could not readily identify, from which crew members the urine in the bags derived. The way the problem of identification was solved was by measuring the concentrations of five different substances in each urine bag and comparing them to samples that had been collected in flight from each bag before trash storage. Each of the samples had been correctly labelled. Since each crew member had a unique pattern of concentrations of the selected substances, the matching and identification of the bags with the samples were possible.

Spaceflight experimentation often requires creative solutions to unexpected problems.

The CVP experiment went well in one astronaut. Originally, we had planned for two astronauts to be instrumented, but unfortunately the catheter broke in one during an extended prelaunch period, where the catheters had been successfully inserted into two astronauts, but where the prelaunch period was extended for 2 days over a weekend because of a failure in one of the shuttle's navigation systems that had to be changed. During some leisure activities, it broke and was withdrawn before launch.

During execution of the experiment on ground before the flight, which is called the baseline data collection to which all in-flight data were to be compared, the biggest obstacle occurred during the execution process of one of the pre-flight test sessions on the ground. The obstacle demonstrated that it is not only a challenge to implement and execute an experiment during the flight phase but that ground tests can be limiting factors too. What happened is that the gas analyser used for rebreathing experiments to determine cardiac output and respiratory variables (**Figure 3**) for some reason did not work. Even though these measurements were not directly involved with our urinary experiment, it sent our experiment to jeopardy, because it was totally integrated into an experimental complement to be executed in concert. The breakdown happened at the Aerospace Medical Institute at the German space centre, DLR, and since the astronauts' test time was extremely limited with many other obligations, it was made clear to the experimental team that the astronauts would withdraw from the experiments, if the equipment was not working the next morning. We knew then that we were in trouble!

We were otherwise all ready to conduct the baseline data collections the next day, and if the gas analyser could not be fixed, it would mean that all of our experimental efforts would go down the drain. What could we do?

Ingenuity, imagination and thinking out of the box are usually essential in solving unexpected problems associated with spaceflight. In fact, this is what characterises this discipline. To my disappointment most of the officials and investigators gave up immediately. It was late afternoon, and the experiments were to be commenced early next morning at 07.00 am. The payload commander had left with a statement that he and his astronaut team would show up on time the next morning, and if the equipment did not work, the experimental complement would be deleted from the mission.

I and one of our ESA representatives soon conferred with each other, and we promised that we would demonstrate to the payload commander that this problem could be fixed in time. The only question was how? At the time we did not know that the problem was a burned capacitor, so we planned to have a technician immediately flown down from the company, Innovision A/S, in Denmark, which had developed and built the equipment.

What we did was risky, unusual and not according to the normal rules and regulations, but we were running out of time. We had to rent a private airplane



Figure 3.

This rack was called Anthrorack and developed for the spacelab D2 mission. It consisted of several pieces of equipment of which one was a mass spectrometer gas analyser used for respiratory analysis and cardiac output determinations by rebreathing (Figure 2). During the ground-based data collections, a capacitor was burned and had to be replaced at a very critical time before the mission.

within a few hours, because there were no commercial flights at that time. We had to establish an ESA guarantee for payment to the airline company, and we—above all—had to get in contact with the technician in Denmark. It soon turned out that he was available and the money for renting the airplane could be secured (after tough negotiations with ESA) and everything seemed possible.

The technician was late at night transported by taxi to a nearby local airport some 200 km away, from where he lived, entered the plane and came to Cologne around 4 am in the morning. We picked him up at the airport in Cologne and brought him to the aerospace facility, and by a miracle, he quickly identified the problem to be a burned capacitor and substituted it by another from a similar equipment.

At exactly 07.00 am before the baseline data collection was to begin, we were ready. The astronauts entered with the expectation that the tests would be cancelled. We could inform them otherwise, and with a rare expression of facial recognition, the payload commander and his fellow astronauts professionally moved ahead to be ready for the tests.

Everything went smoothly!

This as well as the inflight incident with the stuck valve were pivotal obstacles for the outcome of many of the physiological experiments during the Spacelab D2 mission. Had they not been overcome, I would probably not have been able to continue my space physiology career for the next 30 years.

5.7 Data analysis

It is pivotal to make sure that the data collected are correct. One basic rule is for the principal investigator to always be present or to have proper representation at each of the pre- and post-flight experimental sessions and to be monitoring how the data collections are done during flight—preferably from a mission control centre. If that is not made sure of by the investigators of a study, one cannot be sure that the circumstances surrounding the collections are fully understood and that handling of blood samples is done correctly and according to specifications. Furthermore, the investigators have to make sure to be readily available during executions of their experiment should inquiries from space agency representatives need acute responses and interventions. Otherwise, it is unlikely that the data can be trusted.

The investigators must also be proactive and tenacious in obtaining the collected data in space that usually are stored on inflight computers. One way to make sure that the data are correctly handled is to push the mission controllers to download as much as possible from space to ground as soon as the data are collected, because no one knows what could happen afterwards to the storage. Usually, it is not a problem should downloading not be possible, but in this case, it can also delay the post-flight analysis of the data because of bureaucratic impediments to obtain it.

During the very sad and unfortunate accident of the STS-107 mission on February 1, 2003, where the Space Shuttle, Columbia, and crew were lost during re-entry in the atmosphere, I was in charge of an experiment. We conducted inflight cardiac output rebreathing experiments as well as blood pressure monitoring. The data were downloaded to the mission control centre during the mission, which made it possible for us to publish the data so that the experiments—despite the very sad circumstances—were not done in vain.

During the Euromir 95 mission, which was a long-duration mission on the Russian space station Mir, where the ESA astronaut, Thomas Reiter, stayed for 179 days in space, I was in charge of a urinary collection experiment following an oral water load. I obtained the inflight data directly from Thomas Reiter himself shortly after his flight, which is unusual, but we did so to bypass the bureaucracy. Otherwise it could have taken weeks to obtain it.

5.8 Publication

The most important part of all investigations including those in conjunction with human spaceflights is to publish the results in as widely distributed scientific journals as possible. The whole purpose of obtaining the data is to gain new knowledge, and by publishing in science journals with external peer review, there is a certain guarantee for data quality and interpretation. It usually takes 2 years after the end of a spaceflight mission to have the data published, but many times, it takes longer. The investigators, however, owe it to everybody involved as well as society in general to produce a scientific publication as fast as possible.

From the Spacelab D2 mission in 1993, our research team succeeded in publishing three papers within 3 years of the mission [1–3]. During later missions on the Russian space station Mir, the Space Shuttle Columbia (STS-107) and the International Space Station, we conducted five additional experiments focusing on how the human cardiovascular system adapts to short- and long-duration flights [6–10]. This is important for understanding the long-duration health effects of future deep space missions that may last up to 3 years on a mission to Mars.

6. Parabolic flights

In preparation of the CVP experiment for the Spacelab D2 mission, we in 1991 participated in a series of ESA-funded parabolic flights at an air base in Bretigny-sur-Orge, near Paris in France. The purpose of participating in these flights was not only to test the technical feasibility of the equipment in weightlessness but also to obtain short-term data during this condition and compare them to longer effects of spaceflight (see **Figure 4**). At that time, the parabolic flights were conducted by a Caravelle, which flew in a Keplerian trajectory, thereby creating a free fall condition (0 g) symmetrically around the top of the trajectory for 20 s. Some 20 s before and after the 0 g period, the plane underwent a period of increased g's from 1 up to 2. Thus, it is a very short period of weightlessness that is created in this way, but it is the only way to induce real weightlessness in humans without going into actual space.

The CVP equipment was also tested during longer weightless periods (some 60 s) in a fighter airplane (Draken) in Denmark in one of the investigators. This test was supported by the Royal Danish Air Force. All of these tests were conducted in seven subjects (Caravelle) and in an additional one subject (Draken) and demonstrated that the equipment worked during short-term variations in g's between 0 and 4. In addition we obtained data on effects of short-term changes in g-loads on CVP including effects of weightlessness for comparisons with spaceflight.

For further interpretation of the data, we later after completion of the D2 mission performed another series of CVP experiments during 20 s of weightlessness during parabolic flights [11]. In that context, we added measurements of oesophageal pressures through an air tube that was swallowed by the test subject



Figure 4. Dr. Regitze Videbaek measuring the size of the heart chambers in a subject during an ESA parabolic flight campaign. The airplane ascends into a parabolic (Keplerian) trajectory to create weightlessness for 20 s. The subject is also instrumented with invasive monitoring equipment for estimating central venous pressure (CVP), which was also used for the D2 spacelab mission in 1993 on board the space shuttle Columbia [3].

through the nose for obtaining intrathoracic pressures. Intrathoracic pressures are the pressures surrounding the heart. Those pressures were not measured during the Spacelab D2 mission, so the parabolic flight data helped us interpret the CVP data from space.

The process of getting access to parabolic flights is not very different from getting access to spaceflight. Investigators must usually respond to solicitations put forward by a space agency and go through the scientific selection and feasibility assessment processes. The space agency will supply the investigators with the infrastructure such as the flights, but investigators must find their own funding, which usually also applies for adjustments of the equipment to fit into the airplane. In some cases, investigators will have more direct access to the parabolic flight venue, if their experiments concern technical feasibility assessments for a spaceflight. Obtaining experimental baseline data from these flights for comparisons with space data can also be allowed at the discretion of the relevant space agency.

7. Results and conclusions

7.1 Spacelab D2 mission

From the Spacelab D2 mission, our CVP and urinary experiments showed us a new mechanism as to how blood and fluid are shifted from the lower to the upper portions of the body in weightlessness and that the excretion rate of a saline load is not faster than on Earth. Both results were surprising and revealed new insight. Likewise, it was a surprise that the agitating (sympathetic) part of the autonomous nervous system was stimulated during weightlessness and that it was not—as expected—suppressed. In ground-based simulation studies using 6⁰ head-down bed rest or acute seated head-out water immersion, the opposite is usually seen. Thus, there is a difference in effects of weightlessness in space and the simulation models on the ground.

Despite the upward blood shift to the heart and head, CVP was measured to decrease in space compared to being horizontal supine on the ground (see **Figure 5**). We had expected it to be increased. The data we obtained were only from one astronaut, but a US-led team during two other missions also measured CVP directly with invasive catheters and found decreases. We thereafter performed a parabolic flight study and measured CVP with same technology as during the D2 mission and found similar acute decreases during the 20 s of weightlessness [11]. However, we also observed that the heart was expanded despite the decreased CVP, because simultaneously the oesophageal pressure also decreased and even more so. From ultrasound images taken of the heart during the parabolic weightless period, we observed an expansion of the cardiac chambers, so the ostensible discrepancy between the decrease in CVP and the expanded heart could be reconciled by the expansion of the thorax that further stretches the heart and gives an erroneous impression of the change in its feeding pressure (CVP, **Figure 6**).

7.2 Subsequent space missions

From our later inflight experiments [6–10] following the Spacelab D2 mission, the main conclusions can be briefly summarised as follows:

- Cardiac output and stroke volume increase by some 35–40% during months of flight in space, which is caused by the weightlessness-induced upward fluid shift.

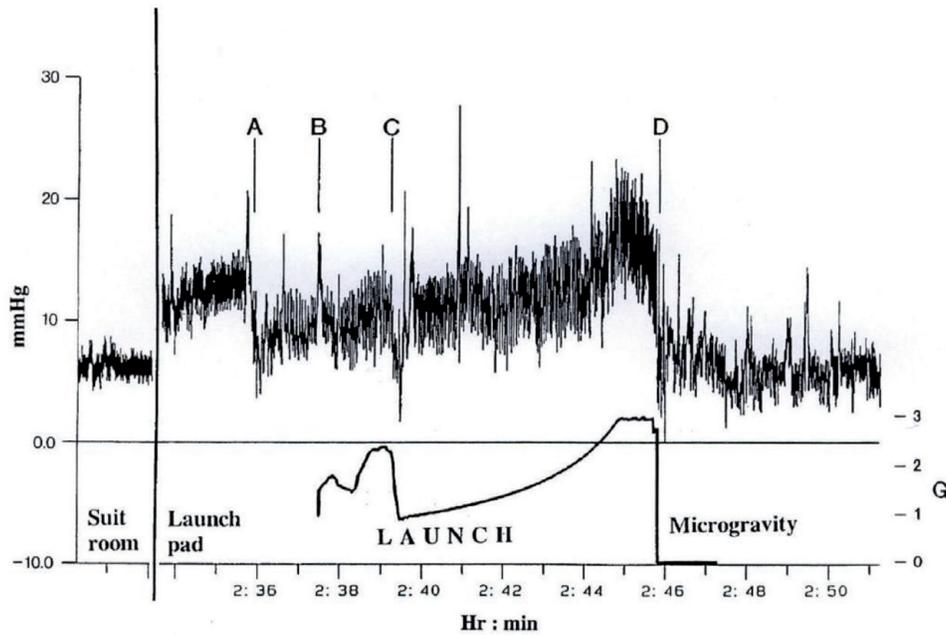


Figure 5. Central venous pressure (in mm Hg) as a function of time in one astronaut before launch of the space shuttle in the suit room with the space suit on and in the shuttle on the launch pad in the supine leg-up position. (A) Closing of the helmet visor. (B) ignition. (C) Release of the solid rocket boosters from the ascending shuttle. (D) Entering weightlessness. The g-load (G) is indicated at the bottom [3].

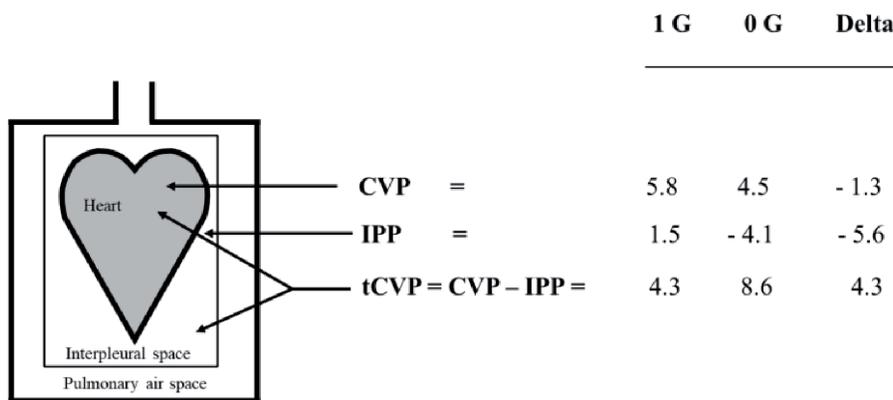
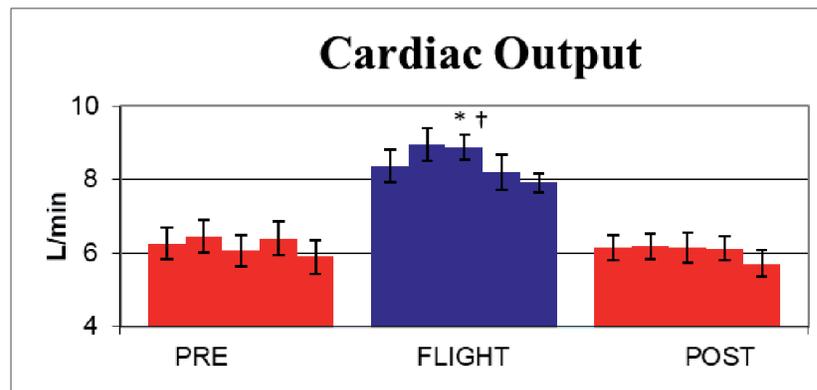


Figure 6. The parabolic flight experiment which helped us interpret the Spacelab D2 mission data. Central venous pressure (CVP) was measured directly with long catheters with transducers at their tip placed near to the heart chambers in supine subjects during the parabolic manoeuvre. Simultaneously, the intrathoracic pressures (IPP) were also measured through long air-filled tubes with balloons at the end in the oesophagus. By subtracting IPP from CVP, the transmural heart distension pressure (tCVP) can be estimated. As can be seen, the tCVP increased in weightlessness (0 G) by 4.3 mm Hg (Delta) even though CVP fell by 1.3. Thus, parabolic flight data could help interpret those obtained during spaceflight [3, 11].

- The arterial resistance vessels dilate and decrease the circulatory resistance by some 40% and blood pressure by 10 mm Hg.
- The sympathetic nervous activity is not decreased in space and is at the level of being upright on ground, which is supported by the attenuated urinary excretion rates of fluid and sodium.
- The dilatation of the arteries and the high sympathetic nervous activity is in contradiction to each other, and the mechanism is not yet known (Figure 7).



Plasma noradrenaline:

730 ± 130 720 ± 90 730 ± 100

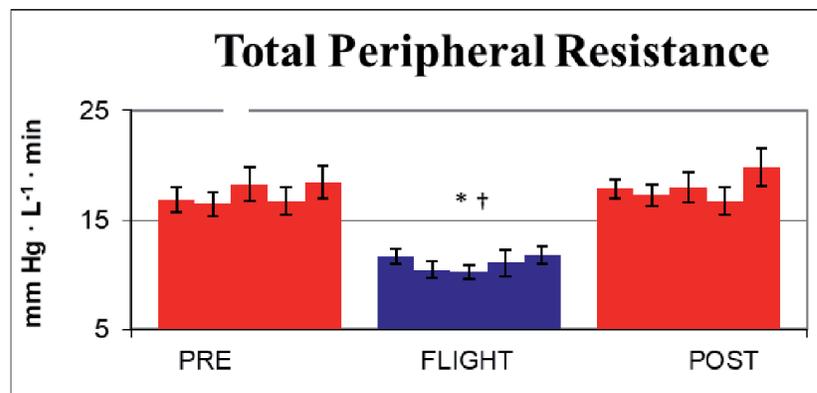


Figure 7.

During missions to the international Space Station in the period of 2006 to 2012, we conducted measurements of cardiac output by a non-invasive rebreathing method in eight astronauts and found a clear-cut increase in some 35% between the 3rd and 6th month in space [10]. At the same time, blood pressure is decreased, which indicates that the total vascular resistance is decreased by almost 40%. In contradiction to this, noradrenaline levels are not suppressed but maintained unchanged from ground-based upright levels. Thus, the mechanism of chronic peripheral vasodilatation in space is still unknown [10, 12].

Thus, to our experience, experiments in space have revealed some new insight and mechanisms into human physiology, which could be of importance in interpreting the health consequences of long-duration flights in the future. By comparing the effects of long-duration (3–6 months) spaceflight on the International Space Station [12] with those of short-term shuttle flights [8], there are at least two important and surprising observations: (1) The shift of blood and fluid from the lower body segments into the heart, which increases cardiac output, is even bigger, and (2) blood pressure is more decreased by a more pronounced peripheral vasodilatation (**Figures 6 and 7**).

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