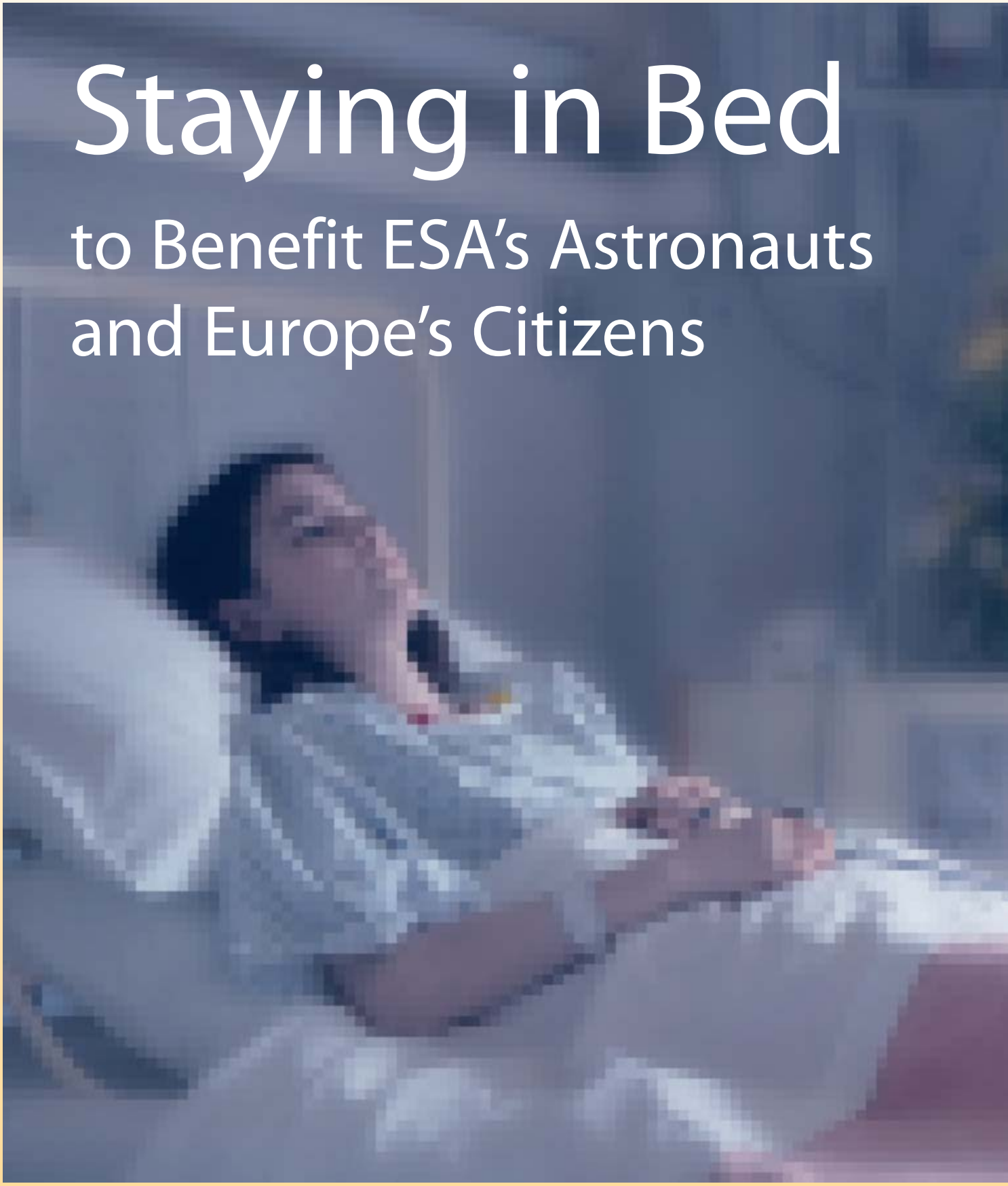
Staying in Bed

to Benefit ESA's Astronauts and Europe's Citizens



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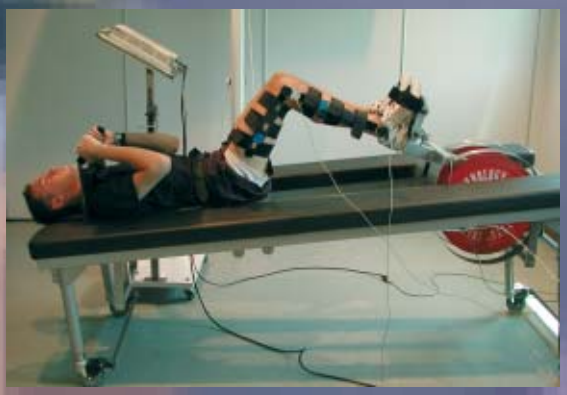


Introduction

Since Yuri Gagarin's historic first flight into space in April 1961, it has quickly become evident that the space environment influences the human body in many different ways and causes it to adapt in ways that can lead to problems when returning to Earth's gravity. Much research has been performed in the meantime and our understanding of what happens to our bodies in space improved considerably during the Mir space station and Space Shuttle/Spacelab era. However, many questions, particularly regarding how to counteract those changes that we now know take place, still need to be addressed through studies on the International Space Station (ISS) and through simulations on the ground.

As we enter an era in which crews will spend longer periods in space on the ISS and of longer term plans by almost every space-faring nation for missions to Mars, it is clear that much more knowledge is needed, and quickly. Although a few hundred men and women have already travelled into space, the operating environment severely limits the amount of systematic research that can be performed - a situation that is unlikely to change. Other avenues for addressing specific scientific questions in a controlled research environment must therefore be found.

One of these complementary alternatives is head-down-tilt bed-rest studies in which volunteers are confined to beds that are tilted –6 deg below the horizontal at the head end. Every activity, including eating, reading, showering, etc., is performed in this position for the duration of the study. This leads to changes in the human body that are very similar to those seen during spaceflight, such as bone-mass and muscle-mass loss, cardiovascular and neuro-sensory de-conditioning. The controlled bed-rest setting therefore allows meaningful research into the bodily consequences of spaceflight and possible countermeasures. It also gives the scientific community interested in space-related medical research more ready access to a clinical model.

The benefits of these studies go far beyond their space application. Patients bed-ridden because of illness or accidents suffer the same symptoms and can thus also profit from the studies. As a clear indication of this link, the clinicians and researchers involved in the bed-rest campaigns typically spend the majority of their time exploring 'terrestrial' problems.

A Medical Challenge for Europe

The long-duration bed-rest study performed over the last year was an initiative of the International Space Life Science Working Group, involving ESA, CNES and NASDA. Lasting 90 days and with 25 test subjects participating, it was certainly a very challenging endeavour. Over 1000 candidates applied, 120 of whom were medically and psychologically screened. Sixty-six scientists from more than 30 research centres in 8 ESA Member States took part, and 20 hospital laboratories and units were involved on site. About 250 people were involved in organizing the study, including 140 doctors, nurses, physiotherapists, psychologists, para-medics, nutritionists, and technicians who were present at the MEDES clinic for various periods during the two study phases.

The amount of scientific data collected is equally impressive: during the study 4350 tubes of blood samples were drawn, plus 825 during the follow-up period, 5500 urinary assessments were made, plus 500 during follow-up, and the blood pressure of each volunteer was taken 250 times. Altogether, about 1000 hours of testing were performed on each volunteer, 43 750 Magnetic Resonance Imaging (MRI) scans were made, etc.

How Our Bodies Change in Space

Some of the most significant adaptational features known to occur when space crews are exposed to microgravity for long periods are:

- Major changes in the circulatory system, such as altered blood pressure and heart-rate control and pulmonary function.
- Decreases in muscle mass and in the neuronal control of muscle activity.
- Differences in posture and locomotion control.
- Altered perception and cognition strategies of the brain.
- Bone loss, exceeding 1% per month in weight-bearing bones, in addition to potentially unrecoverable changes in bone structure.
- Changes in metabolism such as nutrition absorption and control of water and salt excretion.

The bone and muscle changes, which are the most challenging when contemplating long-term spaceflight, were the prime focus of the bed-rest study. In addition, the physiological parameters pertaining to circulation, sleep quality, fluid intake, standard blood parameters and general activity patterns were carefully monitored. Such basic parameters as body weight, blood pressure and temperature were also tracked.

Maintenance of muscle function and bone strength would be crucial for trips to Mars, for example, which would last some 500-550 days, with about 170 days of exposure to microgravity in the spacecraft in each direction, and the rest of the time being spent in the 0.38 g of Martian gravity.

The Study and Its First Results

The first period of the study was completed just before Christmas 2001 and Phase 2 began in March 2002. At the time of writing, the first scientific findings have been presented. The details of the bed-rest study itself were presented in ESA Bulletin No. 108, in November 2001.

Three groups of volunteers (seven, nine, and nine subjects, respectively) were selected: the first group was to undertake a specific exercise programme using the flywheel resistance device selected for flight on board the ISS, the second was to receive one-time medication against loss of bone material (explained later), whilst the third was to function as a control group, neither taking exercise nor receiving any medication.

All three groups received identical nutrition, calculated on the basis of individual pre-study bodyweights, and following general international guidelines from the World Health Organization, to ensure that no weight variations would be due to over- or under-nourishment.

The state-of-the-art clinical diagnostic tools applied in accurately monitoring the changes in muscle and bone tissue for all three groups included Magnetic Resonance Imaging (MRI), two levels of Quantified Computer Tomography (QCT and pQCT), as well as Dual X-ray Absorptiometry (DEXA), which allows the total mineral content (BMC) of the body's bone skeleton to be estimated very accurately.

The early study results are extremely illuminating in terms of the counter-measures applied, looking at the summary data only in the following areas:

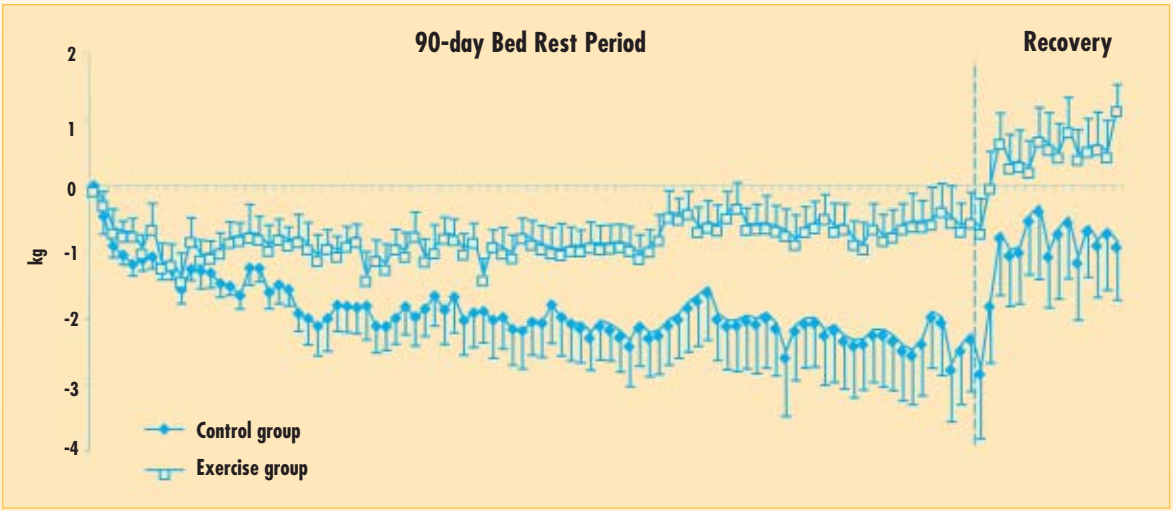
- body weight
- muscle mass and function
- bone mineral content
- gait (walking) and balance
- food absorption.

Monitoring bodyweight

The group that undertook 20 mins of intensive exercise over one hour two to three times a week maintained their bodyweight better than the other two groups. The spread within the non-exercising group becomes larger over time, which indicates a cumulative effect, or rather that these persons continue to lose weight, whereas the exercising group seems to loose the entire amount during the first 10-15 days, and thereafter remains constant.

The data also indicate another interesting trend, namely that the spread in weight data, i.e. with some losing much more than others in the same group, is much larger in the control group than in the group that exercises. Interestingly, this would seem to indicate that the regulation of bodyweight is better when the body burns energy, with energy-demanding activity maintaining the weight parameters within a much smaller tolerance.

Likewise, long-term bed rest leads to loss of body-weight in patients, which is known to be a significant problem in the elderly in particular. This alone can be life-threatening in relation to long-term sickness. Short bursts of maximum-intensity exercise may therefore be a potential countermeasure.



Changes in volunteers' bodyweights during the study, compared with the non-exercising 'control' group

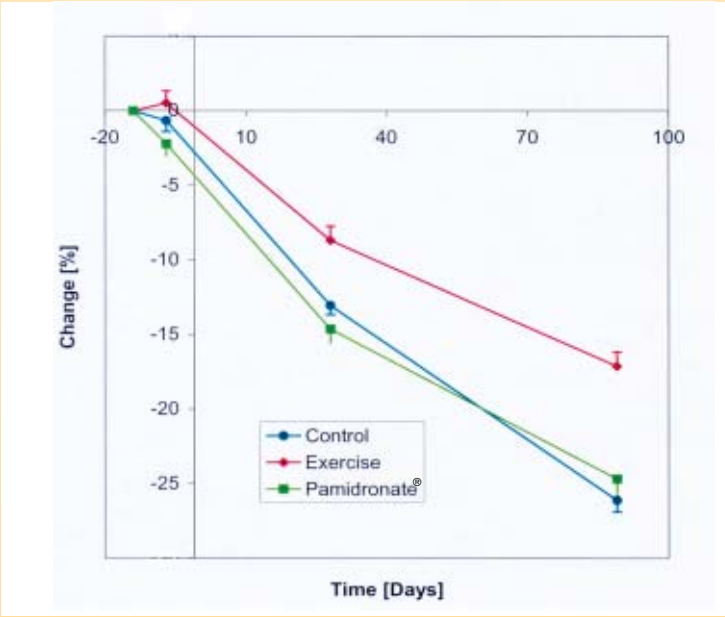
Preserving muscle mass

Due to the sophisticated methods applied in our study, one can discriminate very well between the effects on bone and muscle tissue of preventive medication and of exercise. This allows us to draw clear conclusions as to the next step in defining suitable countermeasures for the negative effects of microgravity.

The exercising group basically preserved their thigh muscle mass almost 100%, whereas the non-exercising groups showed a significant loss. The calf muscles showed a less good result with the current protocol, although exercise helps reduce the loss of calf volume by some 50% compared to the non-exercising groups. In addition, using the flywheel resistance training device increased the static force of calf muscles compared to pre-study levels. This may be because the average person does not usually train this 'locomotion' muscle using this kind of high-output exercise.

The question that still remains is the lack of maintenance of muscle volume, which is probably because the type of exercise applied provided insufficient stimulus for that muscle, which is mainly composed of 'slow fibres'. This suggests that the exercise regime applied is not sufficiently appropriate for training that muscle.

The accompanying illustration shows the relative changes in calf-muscle cross-sectional area (CSA) during 90 days of bed rest. The reduction in CSA is significantly smaller in the exercising group than in the other two groups.



Changes in calf-muscle cross-sectional area as measured by peripheral Quantified Computer Tomography (pQCT) for the three groups

Maintaining cardiovascular function

The resistive flywheel exercise seems to provide no protection against orthostatic intolerance when returning to the vertical again after the bed rest. This intolerance, which affects 50% of astronauts post-flight, means that sufficient blood pressure cannot be maintained in the standing posture for a period of a few minutes. This is crucial for ensuring the return of sufficient blood to the heart and hence to the brain. No significant effect from this exercise regime on this problem was expected, but it had never been tested before over such a long period.

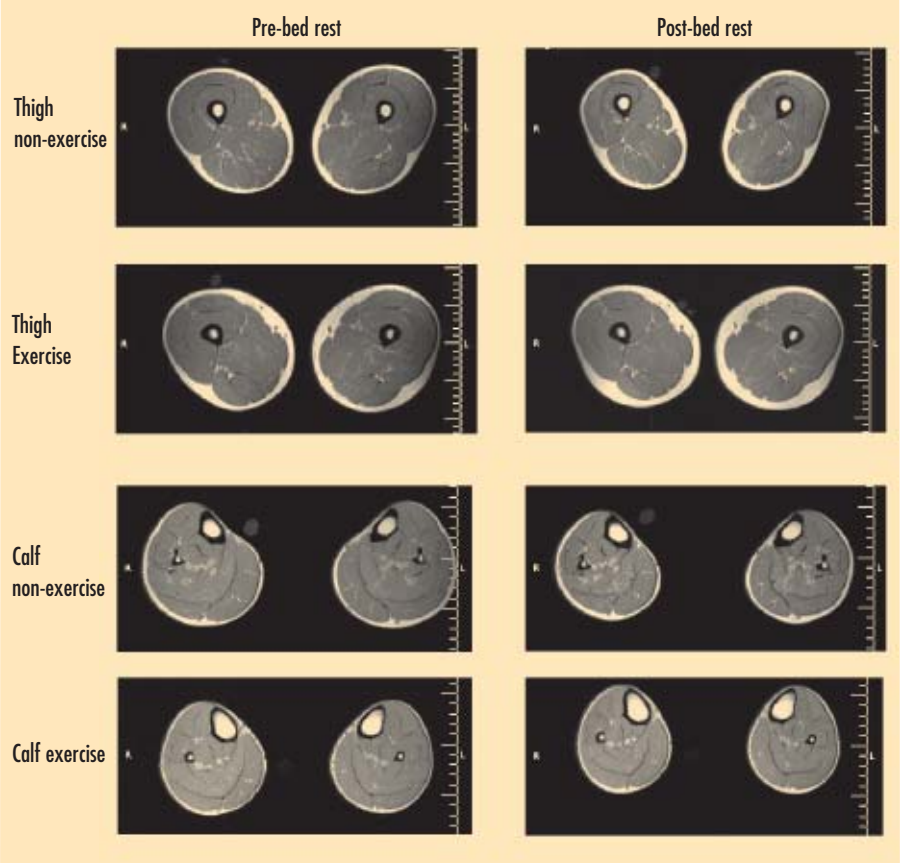
The body's circulatory reflexes rely on a complex system of sensors and effectors, the sensors being pressure sensors in the heart and lungs as well in the large arteries on both sides of the neck. When stimulated, the effectors create appropriate constrictions of the blood vessels, particularly below the level of the heart. This ensures that enough blood is returned to the right side of the heart sufficiently quickly. It is particularly important that these reflexes work correctly in the standing position after a long a time in bed, to avoid blood pooling in regions below heart level, which would lead to insufficient blood getting to the brain and hence to fainting.

Retaining bone structure

Bone development during one's growth years is governed primarily by metabolic processes driven by nutrition and other growth factors. Thereafter one's bones adapt to the changing loading conditions. This process called 'bone resorption' removes bone tissue in one place by 'digging' microscopic cavities, which the bone formation process later refills. In this way, bone slowly adapts to the longer-term loading pattern by strengthening itself where it is most needed.

Calcium is bound into bone tissue in a complex structure, and this is what the traditional screening methods look for when assessing whether or not a person is osteoporotic. Bone mineral content peaks in the early twenties for males, and somewhat earlier for females, and then essentially remains constant for the next 15 to 20 years. Thereafter a natural, age-related slow loss of bone mineral sets in. Post-menopausal women have a much higher risk of developing osteoporosis than similarly aged men, who also tend to have osteoporosis problems much later in life, usually after the age of 65. Osteoporosis therapy is somewhat complicated, as the responses to loading (exercise) or to medication, like the estrogen hormone that plays a significant role in bone preservation, particularly in women, vary significantly from person to person.

Our studies have shown that one type of medication, Pamidronate®, which belongs to the bisphosphonates family, effectively blocks the bone resorption process. In bone detectable changes take place very slowly and are therefore difficult to monitor with non-biochemical methods in the short term. It is however possible after just 24-48 hours to see biochemical changes in the metabolites in the blood as a kind of 'footprint' of the two processes that maintain bone tissue appropriate to the loading being experienced. Both processes, resorption and formation, leave these metabolites in blood and urine, in quantities that reflect in general terms how much one or other process has been active. Bone tissue 'fitness' can be expressed in terms of how well it responds to changing loading patterns, and thus maintains or even increases the bone mineral content, and not least maintains the crucial internal structural arrangement.



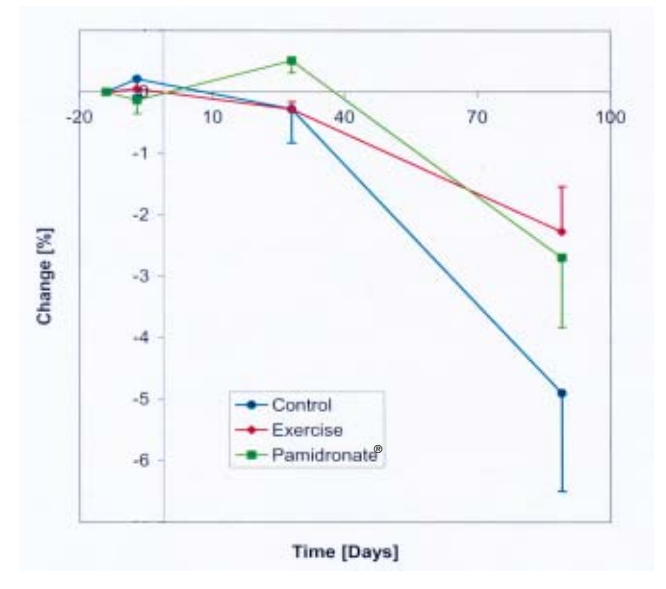
Cross-sectional images of thigh and calf muscles made by Magnetic Resonance Imaging (MRI), showing the effect of flywheel resistance exercise for a typical subject

Our bed-rest study has shown that bone mineral content was significantly better maintained in the group that exercised compared with those who did not. The loading of the large leg muscles even with short bursts of strenuous exercise has a direct conservational effect on bone structure and composition, despite the test subjects being in a near-horizontal position for months on end. This is probably the first well-controlled confirmation for humans of earlier similar findings with animals. The clinical significance of this finding, therefore, is that physical exercise per se is a crucial health-preserving factor for patients faced with long-term stays in bed.

Space experience shows that for some reason the resorption process dominates in weightlessness, leading to a so-called 'negative calcium balance'. There is an accelerated loss of calcium bound into the bone, even when compared to osteoporosis patients. It is assumed that the total absence of gravitational pull on the body when in orbit is the main reason. Hence when people remain horizontal for a longer time on Earth, a similar, although probably less pronounced effect should be observed - gravity is not nullified, but its direction is changed by 90 degrees. The bed-rest study data confirm that assumption.

Regardless of whether or not they exercised, all three groups showed a loss of roughly 0.5% of bone mineral content from the lower leg after 30 days in bed. After 90 days, however, the non-exercising control group had lost 5% on average, whilst the exercising group had lost only around 2%. In addition, a rather large variation between individuals was observed, partly ascribed to genetic factors.

The bone-loss data from the calf bone (tibia) are supported by similar data from the thigh bone (femur), but with less loss in the femur than in the tibia. This corresponds well with the muscle data. What is also very interesting is that exercise had a more constant positive effect than medication, which is probably



Changes in bone mineral content in the lower leg during 90 days of bed rest, as assessed with pQCT. The reduction is clearly smaller both in the exercise group and in the Pamidronate-treated group compared with the control group

due to the slowly diminishing effect of the pre-injected drug over time. Another very important point is that the apparent kinetics and effects of the Pamidronate medication have now been mapped in a bed-rest situation – something that can probably be directly transferred for future bone tissue stabilisation measures for long-term space crews. The clinical applications of this finding are no less important, as such long-term studies on humans with a year-long follow up period have never been performed before.

Does Medication Help?

During the first 30 days of bed rest, the medication, administered once at the start of the study, actually increased the bone's mineral content by some 0.5-1%. This can be attributed to two apparent causes. The first is that it effectively halts the bone resorption process, and as resorption and formation normally more or less cancel each other out the net result is an increase. At the same time, we can conclude that, despite the intense resistance training, which has been primarily designed to maintain muscle mass, over the first 30 days this does not manifest itself in terms of a distinction between the exercising and non-exercising volunteers in terms of changes in BMC, but for the remainder of the study the slope of the loss-curve is significantly smaller for the exercising group than for the other two. Thus although the exercise is primarily designed to maintain muscle, it also has a marked positive effect on bone condition. This is an important new finding, both qualitatively and quantatively, coming out of our bed-rest study.

Finally, without medication against bone resorption, the first 15 to 30 days of an unloading regime seems to be the time constant for a change in BMC of some 0.5-1% to take place. If this is confirmed, the effect of exercise that starts at the outset of the bed-rest period should be visible after that time, which appears likely from the accompanying illustration. Differences in bodyweight development between the exercising and the control groups are already visible some 10 days into the bed-rest period, whilst the BMC data show strong dissociations from day 30 onwards.

Other Interesting Findings

- Normal walking after the bed-rest study required 40% more energy! This is an important indicator of the difficulties to be expected after long-term bed rest or a long space flight.
- The locomotion pattern was changed, being less coordinated and efficient than normal. Running was basically not feasible at all.
- Muscle fibres seemed to become shorter, and their angle of insertion into the tendon plate became smaller. The result was a reduced momentum.
- Exercise seemed to have an impact on how many naps the volunteers needed - maybe another positive effect of exercise in the bed-rest situation.
- Oxygen uptake, a measure of overall fitness, was reduced by around 30% in all groups after the bed-rest phase.

Do Genetics Play a Role?

A potentially important factor, the genetic profile, has not yet been addressed. The volunteers were not genetically tested prior to the study. Between the definition of the experimental programme and finalisation of the study, however, it was decided that this was a potentially interesting area of research if certain genes could be shown to be associated with high or low responses to exercise. Genetic screening is therefore being performed retroactively, but those results will only be available later.

Conclusion

The long-term bed-rest study that has been described here is unique and clearly a first from a duration and completeness point of view, a fact widely acknowledged by the considerable press coverage that it attracted. It will also be a first from the scientific results point of view in that we expect it to generate several tens of publications in the scientific literature. Similar cooperative long-duration bed-rest initiatives with NASA are already under discussion. ESA's planned long-duration bed-rest study with female volunteers in the coming year is the next logical and necessary step, thereby consolidating the Agency's leading position in this area of research.

Acknowledgement

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