Monitoring the cerebral venous drainage in space missions: the Drain Brain experiments of the Italian Space Agency

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Abstract

It is well known that the space environment induces major alterations to various human physiological systems, determining a general deconditioning of the body. Medical research programs aim to keep the astronaut's health status during the mission, enable their ready operation once they arrive at their destination, and allow their safe recovery when returned to Earth. Among the programs coordinated and supported by the Italian Space Agency (ASI), the experiments called Drain Brain, performed by the University of Ferrara, are particularly relevant in this respect. The project, which began with the collaboration of Samantha Cristoforetti in 2014, has demonstrated the capability of a plethysmograph system to study the cerebral circulation and the venous return from the brain to the heart, onboard the International Space Station (ISS). Demonstrating the progressive reduction of the cross-sectional area of the internal jugular vein, particularly significant between pre-flight data collection and the last assessment after 6 months of flight on the ISS ($p<0.001$).

Over the next two years, thanks to the Drain Brain 2.0 project, crews of the International Space Station will be studied with a new version of the plethysmograph, synchronized with the electrocardiogram, to assess cardiac efficiency and brain drainage in relation to symptoms such as blurred vision, numbness, or the feared onset of jugular thrombosis, that is linked to blood flow slowdown due to the absence of the gravitational gradient. Drain Brain 2.0 will also generate important returns to Earth, closing the virtuous circle of terrestrial application of space research.

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Present and future of human space exploration

Human and robotic space exploration is one of the main goals of the space agencies, which have been meeting since 2006 in the framework of the International Space Exploration Coordination Group (ISECG). As part of its activities, the ISECG has drafted and keeps updated the Global Exploration Roadmap (GER), in which the space agencies' interest in expanding the human presence in the Solar System is stated, starting with the currently exploited International Space Station (ISS) and continuing with missions to lunar orbit, then to the surface of the Moon, and finally to Mars.[1,2]

In this context, NASA has established the Artemis program that will initially bring astronauts to lunar orbit (onboard the Lunar Gateway) and lunar surface and finally will enable sustainable lunar exploration. The Artemis missions will allow to perform scientific research, test new technologies, and learn how to sustain human life in the extreme space environment in preparation for human missions to Mars (Figure 1).

Traveling to Mars: risks and challenges

It is now well known that spaceflight induces major alterations in several human physiological systems and that these adaptive responses result in a general deconditioning of the body, that can be assimilated to an accelerated aging process on Earth, with negative impacts on the astronaut's performance and health. Pathophysiological changes induced by the space environment, so far studied in the context of relatively short missions conducted in low Earth orbit, could become even more relevant in long-duration missions to the Moon or Mars. Scientists have identified five categories of human health risks that astronauts will face on a mission to Mars:[2]

i) Cosmic ionizing radiation. Crews are subject to penetrating, steady, low dose-rate exposures and intermittent bursts of high-fluence solar particle events. Humans exposed to this radiation environment are subject to damage to the central nervous system and DNA, thus causing an increased risk of developing cancer, as well as possible reduction in motor function and behavioral alterations.

ii) Gravity. On orbiting stations, astronauts are subject to microgravity conditions. Bones, muscles, and the cardiovascular system undergo major alterations due to the apparent weightlessness; upon their return to Earth, ISS astronauts undergo a lengthy rehabilitation process, in which they are followed by a team of specialists. But when the astronaut, landing on Mars after a journey of about six months in a weightless condition, faces a gravitational field that is 1/3 of that on Earth, need to be promptly able to carry out the mission tasks. This aspect poses a great challenge to human physiology scientists, who have to identify effective countermeasures to minimize the musculoskeletal and cardiovascular system deconditioning induced by microgravity, reducing the need for rehabilitation.

iii) Isolation and confinement. They disrupt the human psychological and physiologic balance, inducing neurocognitive changes, fatigue, misaligned circadian rhythm, sleep disorders, altered stress hormone levels, and immune modulatory changes.

iv) Distance from Earth. It causes both a complication in the management of emergencies and the inability to have continuous supplies from Earth, with obvious implications of both technical and psychological nature.

v) Hostile environment. Ecosystems inside the space vehicle need to be controlled in terms of air composition, temperature, pressure, humidity, lighting, noise levels, concentration of volatile compounds, and microbial contamination. All these aspects play an important role in the crew's health and must be carefully and continuously monitored and controlled.

The combination of all the above-mentioned risks for human space explorations, together with the astronaut's characteristics, determines his or her health risk. Muscle atrophy, bone demineralization, cardiovascular deconditioning, immunological alterations, problems in cerebrovascular and cognitive processes, nutrition as well as alterations in metabolism are the main changes induced by the space environment. Although the adoption of nutritional and pharmacological countermeasures as well as the execution of strict physical activity programs allowed to greatly mitigate the effects produced by LEO missions, there is still much work to do to make long-term human missions beyond low Earth orbit sustainable. In this context, the International Space Station, orbiting at low altitude, is a very useful facility to study phenomena that might occur in missions to deep space.

The International Space Station: an orbiting laboratory for scientific research

The International Space Station is a laboratory orbiting the Earth at an altitude of about 400 km. It is staffed by astronauts of different nationalities, daily carrying out experiments in the fields of biology, human physiology, physics and chemistry, and Earth observation. ISS crewmembers also perform tests to validate new technologies and conduct outreach and educational activities.

The ISS offers the opportunity to carry out scientific investigations in an environment characterized by microgravity and a level of radiation higher than that of the Earth's surface, the Earth's atmosphere shielding effect being absent. Therefore, aboard the ISS, scientists can study the behavior of organisms, the effectiveness of countermeasures against space-induced health issues, and new technologies to facilitate human activities for future deep-

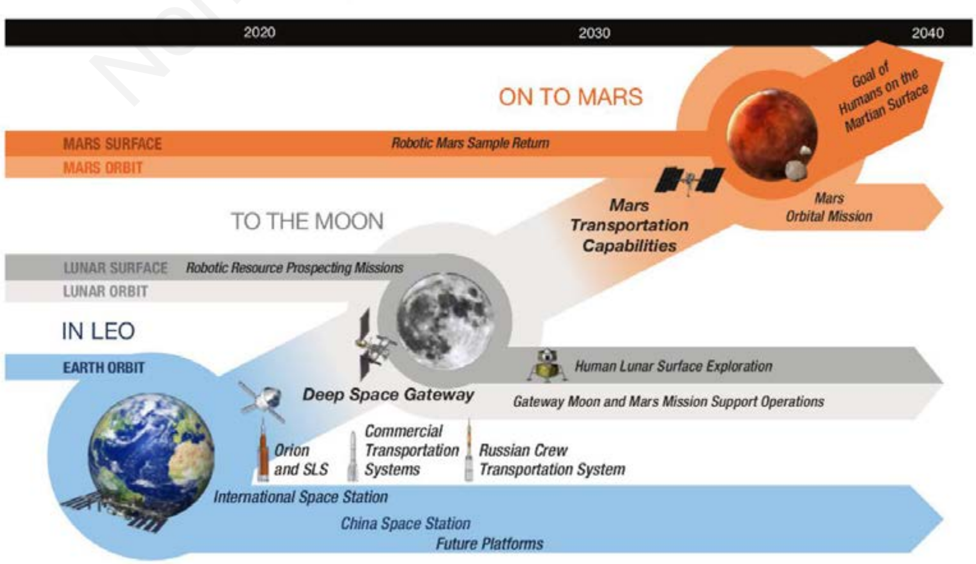

Figure 1. Graphic representation of the plan for human space exploration, taken from the Global Exploration Roadmap.

space long-duration missions. Among the European space agencies, the Italian Space Agency (ASI) has a privileged position within the ISS program. Indeed, in addition to being part of the European Space Agency (ESA), and thus having access to the station's experimental resources under its participation as a European partner in the ISS program, ASI in 1997 signed a Memorandum of Understanding with NASA for participation in the ISS, allowing Italy to access a portion of USA ISS resources for scientific and technological research purposes and to take advantage of short- and long-duration flight opportunities for astronauts of Italian nationality. It was within the framework of this agreement that in 2014-2015 ASI realized a package of seven experiments for Samantha Cristoforetti's Italian "Futura" mission. The experiments, among others, focused on monitoring the astronaut's health status (Drain Brain and Wearable Monitoring), studying specific biological phenomena in weightlessness (NATO, Cytospace, Bone/Muscle Cell), and finally validating particular technologies for space (ISSPresso). Within the studies regarding human physiology in space, those about surviving are considered fundamental. Especially those that, using newly developed sensors, investigate cardiovascular modification, particularly in brain drainage. This is where drain brain trials fit in.

The next sections of this paper will focus on the Drain Brain Project, aimed at studying cerebral circulation and venous return from the brain to the heart, describing the usefulness for human health in Space as well as on Earth and the technological developments being implemented for the future.

Monitoring brain drainage

The blood circulation within our thinking organ is designed to ensure the best possible perfusion of oxygen and the most effective drainage of toxic substances and metabolites. Since the brain is housed inside the cranial box, which obviously cannot expand, Monroe-Kelly's law states that the volume of arterial blood entering it must equal, in the unit of time, that which exits through the venous system. And, indeed, for a biped like man, living with his head above his heart in the presence of gravity is a real cakewalk. Gravity-driven venous blood rushes towards the heart like the water from a fall downstream. Yes, but in microgravity conditions, the favorable gradient disappears, so what happens to our cosmonauts? This is the focus of the Drain Brain experiments, proposed by the University of Ferrara to the Italian Space Agency (ASI): a difficult and challenging scientific journey that began with Samantha Cristoforetti during her long flight from November 2014 to June 2015.

The lack of a proven methodology for investigating cerebral venous return had previously generated considerable scientific controversy, forcing space researchers to start building evidence. Using ultrasound equipment, it is indeed possible to obtain information on a number of quantities related to blood flow, in particular blood velocity.[4-6] Non-invasive screening tests such as Doppler ultrasound are frequently used for routine investigations to detect flow in individual vessels. Plethysmographic methods, on the other hand, measure flow in the entire anatomical section or volume under examination.[7-9]

Plethysmography is a non-invasive technique for recording volume changes in tissue that, unlike ultrasound, overcomes operator dependence in acquiring the measurement. In particular, strain-gauge plethysmography is used to detect venous abnormalities in the legs, measuring the change in venous volume related to changes in posture and exercise, or even flow blockage due to thrombosis.[7] Recently, cervical plethysmography has also been successfully developed, which can indirectly measure cervical venous blood volume and assess cerebral venous return in relation to changes in posture.[8,9]

The diameter and shape of veins undergo significant variations related to transmural pressure and vascular compliance (as well as compressions from the outside by surrounding muscles and any measuring instruments) that produce oscillations of interest. Brain drainage and cardiac efficiency in humans can be studied through one of these oscillations, called the Jugular Venous Pulse (JVP),[10] whose waveform is an indicator of cardiac function and a prognostic factor in chronic heart failure.[11,12] The internal jugular vein is the only vein in the human body that visibly pulsates to the naked eye. This phenomenon occurs because the jugular vein can be likened to a manometer that is ideally placed in the right atrium of the heart. Every change in cardiac pressure is transduced into a wave propagating along the vein wall in an upward direction, making the vein pulsatile and giving rise to the JVP, a circulatory signal loaded with paramount hemodynamic information. The JVP is thus due to the change in vein wall tension caused by the propagation of the pressure wave, which originates from the right atrial pressure during the cardiac cycle, determining the characteristic pulsatility of the Internal Jugular Vein (IJV) (Figure 2).[11,13]

JVP is a pivotal physiological parameter for assessing cardiac filling, pump function of the heart, venous return, and cerebral drainage. We can probably consider it the main parameter of the so-called heart-brain circulatory axis.

Currently, JVP is qualitatively assessed in clinical practice, but its quantification can only be done by an invasive approach, through jugular catheterization and subsequent central venous pressure measurement. Recently, the research group at the University of Ferrara has taken important steps in the direction of proper assessment of JVP and related parameters. It was discovered, for example, that JVP can be extrapolated from ultrasonographic clips of IJVs (*Appendix 1*).[13,14]

The post-analysis of the sequence of the Cross-Sectional Areas (CSA) modifications for each heart-beat allowed us to build a JVP curve, as shown in Figure 3. The JVP waveform is composed of three ascents and three descents waves, which correspond to the

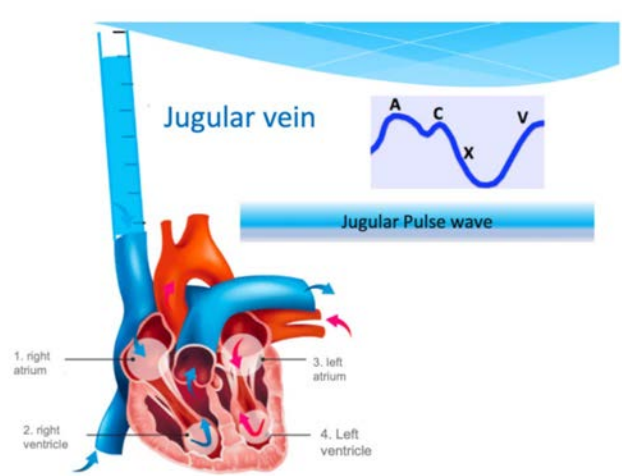

Figure 2. Jugular pulse wave and its peaks.

pressure variation of the cardiac phases: atrial contraction (wave *a*) synchronized with the P peak of the Electrocardiogram (ECG), followed by atrial relaxation (wave *x*) and tricuspid valve closure (wave *c*). After the QRS complex of the ECG, the ventricular systole starts while passive atrial filling occurs followed by pressure drops. Subsequently, after the T peak of ECG corresponding to ventricular repolarization, the maximum atrial filling will be obtained (wave *v*) before the tricuspid valve opening. This latter causes a sudden pressure decrease coincident with ventricular filling (wave *y*), and the cycle will start again.

The accuracy of the curve depends on the resolution of the ultrasound equipment. We need to analyze about 40 different CSA of the jugular vein for each heartbeat to obtain a very reliable non-invasive trace of the JVP.[14] In further experiments, we investigated if the Ultrasound JVP may provide a consistent estimation of central venous pressure.[15] Therefore, the autocorrelation of the Ultrasound JVP with the invasive gold standard was highly positively correlated (mean r=0.725, SD=0.215). Using the lagging autocorrelation r-values as predictors, mean-CVP was predicted with reasonable accuracy (r^2=0.612), with a mean-absolute-error of 1.455 cmH2O, which rose to 2.436 cmH2O when cross-validation was performed (Figure 4).

The problem of the investigators at this point was to obtain similar results by means of a non-operator-dependent device. As a matter of fact, we know that ultrasound is strongly operator-dependent and this could affect the JVP assessment, particularly in a special environment like the spatial mission. To this aim, a special application of the plethysmographic technique has been developed which, using strain gauges, can detect changes in blood volume in the human venous system.[8,9,16] The latter methodology was performed in comparison with ultrasonographic scanning.

The investigators demonstrated that the two traces, acquired with the two different instruments, correspond to the measurement of the same physiological phenomenon, namely the JVP waveform over time. Concerning the temporal distances '*a-a*' and '*v-v*', particularly, the temporal distances between the peaks a and v do not exceed 0.1 s. In accordance, the resulting mean values were satisfactory, allowing us to propose the use of non-operator dependent plethysmography instead of ultrasound: $\Delta t a\text{-}a$=(0.05±0.03)s, $\Delta t v\text{-}v$=(0.04±0.03)s.[17]

Drain Brain, first experiment and outcomes

As already described, cerebral venous return is strongly influenced by the gravitational gradient in the upright position while, in the supine position, it is linked both to the atrial aspiration and the thoracic respiratory pump (*vis a fronte*). Little is known about the mechanisms ensuring the blood outflow from the brain in microgravity conditions. The efforts of the research group at the University of Ferrara were enhanced in the Drain Brain Project, which was successfully carried out as part of the 'Futura' mission on board the ISS. During Drain Brain, the functionality of the circulatory system of an ISS crew member was evaluated both on Earth and in microgravity conditions. The project was funded by ASI, and the experiment was coordinated by PI Paolo Zamboni of the University of Ferrara. The plethysmography developed by the research team, based on a strain-gauge extensometer, was tested by Samantha Cristoforetti, an astronaut of the European Space Agency, during her first long-duration mission on the ISS and by volunteer subjects on Earth.[13-16] The experiments were conducted by measuring JVP from high-resolution ultrasound clips performed by the astronaut herself. In summary, the main results of the experiment were the following: i) the awareness of the JVP phenomenon also in the micro-gravity condition, because it was never previously detected in the ISS experiments; ii) the progressive reduction of the IJV-CSA, which was prior to Drain Brain experiment postulated to be increased in microG; this effect is the consequence of the continuous dehydration occurring a space mission lasting several

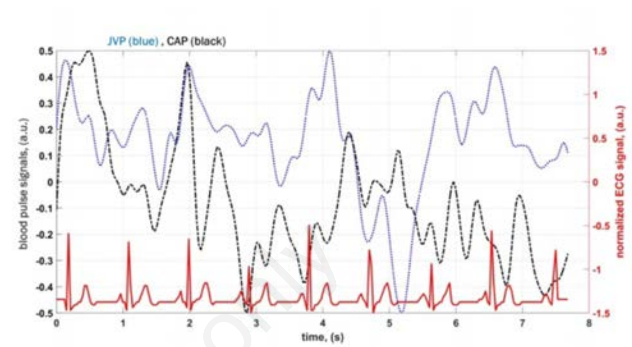

Figure 3. The acquisition of blood pulse signals over the neck area with Electrocardiogram (ECG) synchronization. The acquisition was performed with an ultrasound scanner using a linear probe on the right side of the neck of a supine subject. As for the visualization of the signals in Figure X, they were normalized and plotted in the amplitude range of -0.5 to 0.5 for the blood pulses, and from -1.5 to -0.5 for the ECG. About the blood pulse signals, the dotted blue curve is the Jugular Venous Pulse (JVP) waveform, and the dashed black curve is the Carotid Artery Pulse (CAP) waveform. The red curve is the electrocardiogram signal.

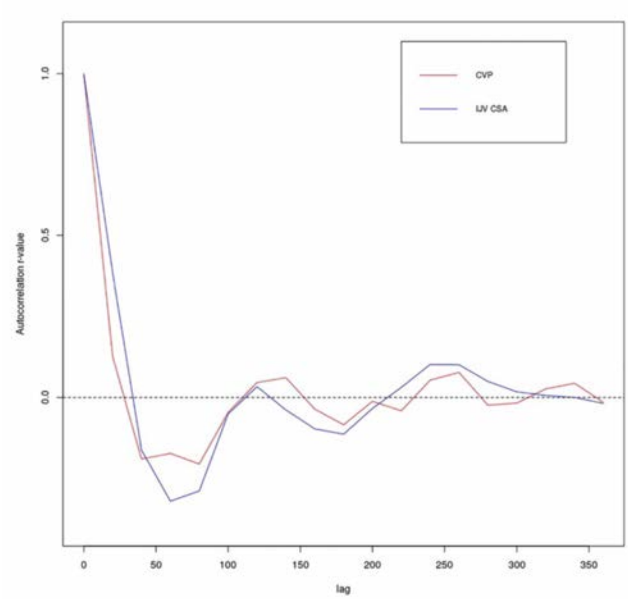

Figure 4. An autocorrelation graph clearly demonstrating the significant overlapping between the Ultrasound JVP non-invasive assessment (blue line) as compared with the gold standard invasive measurement of Central Venous Pressure (CVP, in red line).

months; in Figure 5a, the significant and progressive reduction of the "peak a" is well apparent; iii) the progressive reduction of the Δ, *i.e.* the difference between the highest and the lowest JVP peaks, respectively "a" and "x". Da seems to represent the true effects of the microG on the JVP because the reduction happens immediately once the astronaut enters into the ISS and return to the base level shortly after the landing, as clearly shown in Figure 5b.[13] Worth note, the ultrasound experiments were carried out with simultaneous acquisition of plethysmographic signals, performed under different respiratory, postural, and exercise conditions. The comparison between the US and plethysmography signals performed at the end of the mission makes the researchers aware of the highly significant correlation between the two methods of assessment. Strain-gauge plethysmography is a non-invasive technique that, by means of a sensor surrounding the neck, records changes in electrical parameters (*e.g.* capacitance) determined by deformations induced on the sensor by changes in jugular vein volume. This measurement methodology is ideal as it is non-operator-dependent and non-invasive.

The novelty of the device lies in its ability to detect oscillations of the neck veins with enough accuracy to be useful for studies concerning cardiac oscillations. This is possible thanks to extensometric sensors powered by a constant current, which allows the electronic system to detect changes in the length of the sensor by measuring the charging time of its capacity.

It has already been demonstrated by the research group of the University of Ferrara that this system can detect changes in the area with sufficient sensitivity to also record fluctuations in blood vessels of interest.[18] During plethysmographic studies on healthy subjects, it was shown that a change in posture from upright to supine produces an increase in the perimeter of the neck, thus confirming that the IJV is the main outflow pathway for the brain in the supine position. Furthermore, an increase in pulsatility was found for all subjects in the supine position, a result in agreement with Magnetic Resonance Imaging (MRI) studies that showed that venous outflow from the brain is much less pulsatile in the upright position.[19] As this pulsatility is intimately linked to the structure of the vessel and the heartbeat, it represents a very characteristic signal to be studied and correlated with other recognized signals in physiology.

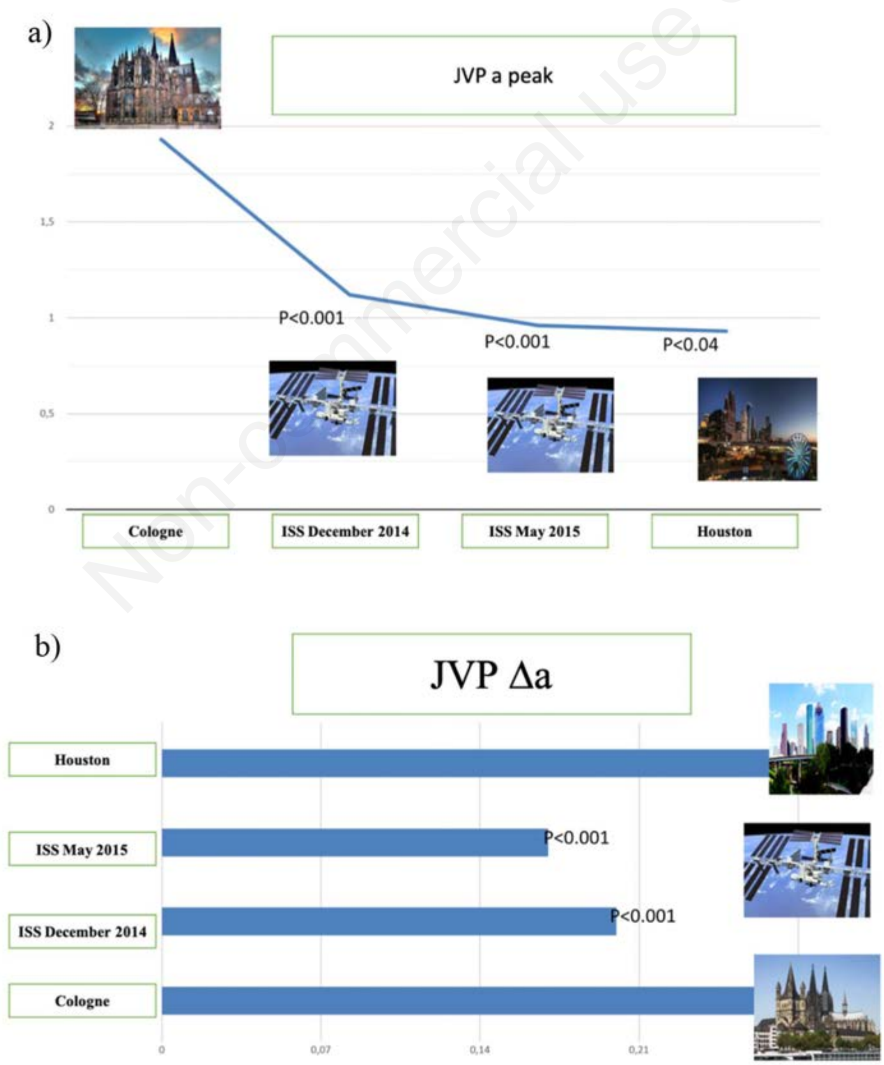

Figure 5. a) Progressive reduction of the "peak a"; **b)** Δa variations.

Future projects Drain Brain 2.0

The keystone of the Drain Brain study occurred when the researchers analyzed the data obtained on Earth and realized that the plethysmographic signal also contained the JVP trace, which, as explained above, was simultaneously obtained by the astronaut with the onboard ultrasound scanner. Continuing the experiments on Earth, the reliability of the JVP plethysmographic survey compared to the ultrasonographic one proved so satisfactory that the researchers proposed to conduct the subsequent experiments with the plethysmograph alone, albeit technologically advanced (Figure 3). The Drain Brain 2.0 project, supported by the ASI and started in March 2022, proposes to develop a new, space-saving strain-gauge plethysmography system with ECG synchronization and use it in space both to study cerebral venous return in microgravity conditions and to understand physiological adaptation mechanisms of the heart. Synchronization with the ECG trace is indispensable for at least three reasons: A. The time variable of the JVP graph is normalized to the heart rate of each individual test subject B. Identification of the JVP peaks is facilitated by the temporal correspondence with the ECG trace C. In perspective, the test represents the basis for constructing models of the heart-brain circulatory axis under microgravity conditions or during long space travel.

The versatility of the new instrument may make it possible to highlight any other problems that astronauts might develop due to weightlessness, such as the development of thrombosis caused by the combination of a slowdown in flow, due to non-terrestrial gravitational conditions, with a state of reduced circulating blood volume due to dehydration that occurs during long space flights.

In light of a recent study conducted on a cohort of 11 astronauts during their stay on the ISS, stagnant or retrograde blood flow was found in the IJV of 6 astronauts, while one of these astronauts had developed thrombosis at the IJV.[20] This serious risk associated with spaceflight, not yet known to the scientific community, has severe implications for astronauts' health and requires urgent in-flight monitoring and possible treatment. Thus, the availability of a new diagnostic tool for the systematic monitoring of crew members' cardiovascular parameters becomes crucial. But, of course, the JVP enables much more. It is not difficult to understand, for example, that a reduced efficiency of the heart pump during long space missions results in difficulty in the disposal of blood returning to the heart with changes in the cross-sectional areas of the vessel that can be measured by JVP plethysmography. Other intuitable fields of application could be the correlations between cerebral venous return and the development of visual or cognitive symptoms in astronauts during long-duration flights: Spaceflight Associated Neuro-ocular Syndrome (SANS) consisting of blurred vision, numbness, and brain fog.[21]

The integration of data from experiments performed both on Earth and in space will be crucial for obtaining information on human physiology. With the Drain Brain 2.0 project, an innovative diagnostic device will be developed and tested on the ISS. The development and space testing of the new instrument is conceptually very reminiscent of what happens in the car industry, where the great innovations tested in Formula 1 are later found in our small cars. In fact, the Drain Brain 2.0 project proposes to use the same device on Earth for clinical use in Telemedicine, since it is an instrument that is already born with ideal dimensions and portability for so-called Proximity Medicine. Compared to today, space innovation could very quickly and decisively impact the needs of patients on Earth, thus providing assistance to populations with difficulties of movement and for whom it is limited to travel to hospitals for a consultation. The economic and social spin-offs of these opportunities are immediate, an example in terms of easing the burden of care for caregivers who no longer have to be diverted from productive and work activities to periodically accompany family members suffering from chronic diseases. Positive spin-offs can also be had in terms of improving cardiovascular fitness, with a wider range of people affected, who for various reasons are forced to reduce mobility and exercise. The instrument can, in fact, be easily used in the field and monitor the progress of therapies based on exercise programs structured for preventive or rehabilitative purposes. The product to be developed for Earthlings' needs is a non-invasive and 'green' system as it does not expose them to the harm of traditional radiology. The new space device will be able to provide expendable information for the study of cardiovascular diseases at an extremely low cost. As mentioned above, ideal candidate fields of application will be heart failure[15] or cognitive problems in the elderly. The new device could also be used to study neurodegenerative diseases, since a pilot study, presented by the University of Ferrara research group at the International Society for Neurovascular Diseases (ISNVD), showed that the jugular pulse waveform exhibited significantly different peak areas in patients in the early stages of Alzheimer's disease compared to control subjects.

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