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# Lymphatic circulation in astronauts: basic knowledge, challenges and perspectives

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**Abstract. – Space missions expose the astronauts' bodies to various stressors, including microgravity. While numerous studies have investigated the effects of this stressor, research on its impact on the lymphatic system remains confidential. This review highlights the importance of scientific research into the human lymphatic system exposed to long-duration space missions. The safety of astronauts is a major issue. Chronic slowing of lymphatic drainage disrupts the balance of fluid and macromolecule exchange within poorly drained anatomical areas. Their extracellular matrix gradually becomes the site of dispersed deposits of degraded proteins and increased local water content. The interaction between these two phenomena leads to mutual amplification, resulting in a slow, gradual increase in pressure within the impacted tissue, which undergoes an expansion known as edema. The speed at which these pathophysiological processes take hold includes the extent of the lymphatic insufficiency and any compensatory measures that may or may not be put in place. Lymphatics are present everywhere in the body where tissues receive blood. Organs such as the brain, heart, and intestines, among others, as well as local immune function, can be damaged over time when their lymphatic system becomes chronically insufficient. The human clinical experience of lymphatic insufficiency tells us that the onset of edema takes time and is an insidious but inevitable phenomenon if adequate compensation does not occur. The time required for the pathophysiological consequences of lymphatic insufficiency to become established does not coincide with the time allocated to bed rest experiments or current space missions. With the prospect of longer space missions, lymphatic insufficiency linked to microgravity could unexpectedly become a major obstacle to human life in space.**

*Key Words:*
Lymphatic circulation, Astronauts, Lymphedema, Lymphofluoroscopy.

## Introduction

The space missions of the future will be spread over much longer periods. They pose the complex problem of enabling human beings to live for longer periods than is currently the case, in an environment that is not a priori conducive to the development and maintenance of life. Astronauts are permanently subjected to a very long list of stressors, such as microgravity, cosmic radiation, changes in the distribution and local composition of body fluids, sleep deprivation, altered circadian rhythms, etc. They must cope with prolonged confinement, dietary

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constraints, significant acceleration and deceleration during launch and landing, constant noise, loss of physiological performance, and psychological stress. This is collectively called "the space exposome[1]". The physiological and molecular adjustments of the human body to the space exposome give rise to pathophysiological conditions, such as bone mass and muscle fiber loss, changes in the lymphatic and cardiovascular circulation, immune dysregulation, and increased risk of cancer[2].

Various studies[3] carried out on the earth during bed rest sessions or in space have led to a better understanding of the phenomena underlying the physiological adaptations to our exposome. Historically, the lymphatic system (LS) has been omitted from the vast amount of research in space physiology and pathophysiology[4]. As one of the vascular systems, it is essential for maintaining fluid and macromolecule homeostasis and the immune system. The LS is an enormously dense network of thin transparent vessels, inhabiting all the tissues that receive blood in the human body. The LS is also subjected to the stressors of the space exposome. Human clinical practice has amply demonstrated that prolonged impairment of lymphatic function in each anatomical area causes a pathophysiological cascade leading to slow, progressive congestion of poorly drained tissues. This cascade then leads to dysfunctions in the affected organ or the impacted anatomical region as a whole. These phenomena occur insidiously without being clinically observable during the subclinical phase, which can take many months before any measurable edema appears[5].

Therefore, we need to expedite further research to bridge the gap in knowledge compared to other systems. The aim of this article is to make researchers in the field of space physiology aware of the tools available and the problems posed by the LS, which are still too often ignored in research planning.

## The Lymphatic System

The tetrad "Extracellular Matrix (ECM) - Microcirculation - Cells and Lymphatics" is a complex system in permanently unstable equilibrium, which maintains local tissue homeostasis. The role of the fourth player, the LS, has been ignored or minimized by most research on human physiology and pathophysiology in space, despite each of the four players being contingent on and regulated by the other three.

There are many reasons for this unconscious lack of interest[4]. Without intending to be exhaustive, we should mention the relative ignorance surrounding lymphology. Even today, basic training programs in medical faculties do not include a course focusing on lymphology. It, therefore, comes as no surprise that, once they are active in the clinic or in research, health professionals repeat the same lack of interest, which results in a lack of curative treatment of lymphedema and lymphatic diseases[6].

Another reason is the transparency of the extremely fine vessels of the LS. As they are invisible to the human eye, they are usually ignored. It has been only for the last fifteen years, thanks to near-infrared fluoroscopy (NIRFLI), a minimally invasive and dynamic imaging tool, that we have been able to observe in a living human, in real-time, with a high resolution, the superficial lymphatics and the lymph bolus displacement into the superficial lymphatic collectors[7].

It is only when the effects of lymphatic insufficiency significantly impact the tissues concerned that people become aware of the existence and the importance of the LS. This manifests by the reduction, often partial, of the local lymphatic drainage, causing the progressive onset of local persistent edema.

Primary and secondary lymphedema in adults could have a relatively long latent period before it exhibits. The LS is not just a hydraulic system, as it is often described in the literature. As one of the key players of the tetrad, the LS resorbs and exports daily from the ECM exchange platform to the bloodstream through a cascade of afferent lymphatic collectors, lymph nodes, and efferent lymphatic collectors[8], most of the excess fluid[9], cells, and metabolic "waste", including hyaluronan[10].

Acting as a garbage collector and transporter, LS is also an essential player in local immunity, contributing to immune vigilance in all anatomical regions. Even slight dysfunction of the local LS, if it persists and is not compensated for, inevitably leads in time to local immunological dysfunction, forcing patients suffering from lymphatic insufficiency to have to manage not only their chronic edema but also the numerous infectious episodes that regularly occur in areas affected by deficient lymphatic drainage. Erysipelas and lymphangitis are indeed common complications of lymphedema[11].

The chronic lymphatic impairment leads to an accumulation of proteins, free water, and a form of jelly composed of water bound with hyaluronan. All these elements contribute to the mechanotransduction phenomena acting in the tetrad, which, through the interactions of integrins and collagen fibers, lead to the slow and progressive geometric deformation of the ECM of the affected organ. This may occur in the cutaneous or subcutaneous territory of a limb, an organ such as the heart, kidneys, or brain, or any other anatomical structure that accommodates blood microcirculation. Within the brain, and particularly in the bone tunnels of the cranium, mechanical conflicts between the container/contents can lead to the compression of noble structures[12].

The lymph of a given territory mirrors its metabolism. For example, lymph from the limbs is very light yellow and transparent, containing a lot of hyaluronan and little lipids, whereas lymph from the mesenteric network, chyliferous, is milky and contains numerous long-chain triglycerides. Impairment of the chyliferous induces edema in the lower limbs but also digestive disturbance, inflammation, and malabsorption of essential nutrients. Once in the lymph nodes, the lymph undergoes complex processes of filtration, degradation, and exposure to immune system cells. Depending on the type of lymph they have to process, the lymph nodes differ in their structure and cellular content[13]. It is here that hyaluronan from the ECM of lymph node-dependent areas is broken down by the macrophagic system[14].

The smallest molecules of this treated lymph go directly into the bloodstream *via* the microcirculation of the lymph node and then from its vein. Larger molecules that are too voluminous to enter the lymph node microcirculation reach the efferent lymphatic collector to continue their journey through the cascade of collectors and lymph nodes. All of this lymph, which has not been able to enter the microcirculation when passing through a lymph node, reaches the thoracic duct, which in turn empties in a particular way into the venous network at the level of the jugular-subclavian venous junctions.

Shortly before it enters the venous network, the thoracic duct follows a route that looks convoluted. In fact, as the thoracic duct runs up the spine, and then veers slightly to the left, a direct connection *via* the lower part of the subclavian vein would seem most logical. However, it rises higher than the jugular-subclavian angle, then makes a 180° turn, and finally ends up vertically above the venous network. This peculiar arrangement has its origins in the embryological position of the lymphatic sacs, but above all, its development is linked to the evolution from quadruped to biped. This adaptation to the field of gravity optimizes the emptying of the lymph into the venous network at this point.

The lymph moves through the lymphatic collectors in boluses. Consequently, there is no constant flow in the lymphatics, as it is widely believed. The lymphatic collectors are thin-walled, collapsible, porous tubes[15,16] whose lumen remains permanently open by suspensors anchored to the outer wall. These translucent vessels have a linear trajectory and a beaded structure. Each "bead" is called a lymphangion. Endothelium[15] folds provide a bicuspid check valve at each end of the lymphangion, preventing fluid backflow.

Smooth muscle cells[17] contribute actively to lymph transport, propelling the lymph bolus by their contraction[18]. Contractions are not rhythmic all along the collectors[19]. Only short sections composed of 2-5 contiguous lymphangions contract vigorously in an ordered sequence to propel the lymph in a centripetal direction. The contraction only starts when the lymphangion contains enough lymph to stretch its endothelium. Relationships between the lymphatic transmural pressures and nitrous oxide contribute to the adjustment of lymphatic pumping[18]. Recently, Cajal-like cells[20] were identified inside the wall of the thoracic duct. They are probably involved in the neuromuscular organization of lymph propulsion. The complex neuro-mechanic transduction response, which provokes and coordinates the lymph bolus propulsion, needs more investigation to be clearly understood.

Lymphangions do not have the energy to contract continuously. After a few consecutive contractions, the lymphangion reaches a fatigue threshold. If the lymph continues to arrive in this lymphangion, it stagnates there until the lymphangion restores its contractile capacities. When we are active, the main driving force behind the movement of lymph in the lymphatic collectors is not the contraction of the lymphangions, but the constant perpendicular stretching and slackening of the tissues surrounding the collectors. Therefore, the intrinsic contraction of the lymphangions can be seen as a backup system when we are immobile or when the environment of the collectors does not allow the full extent of the necessary deformation. The proper functioning

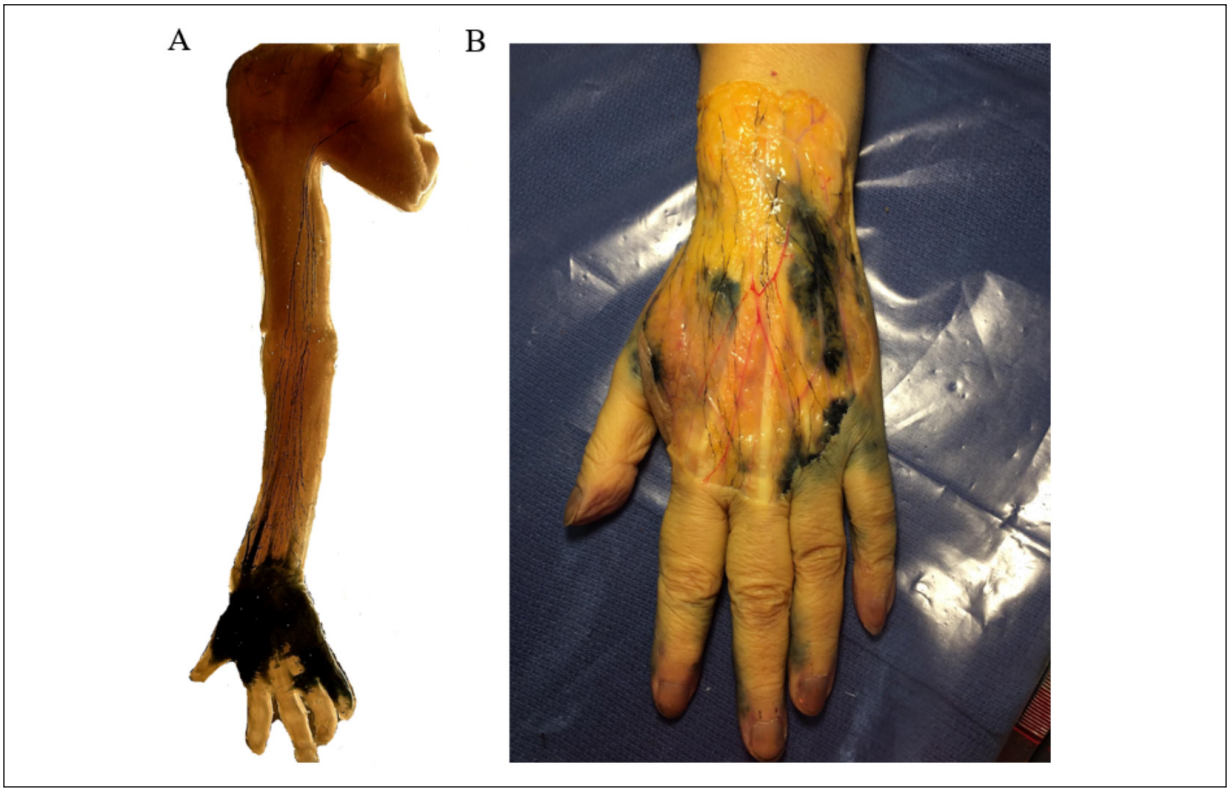


**Figure 1. A**, Superficial lymphatic collectors are numerous at the distality of the limbs; then, reaching the root of the limb, they come together in clusters, reducing their number. Provided by: Pr. M. Amore - Vascular Anatomy Dpt. UCA Buenos Aires - Argentina. **B**, Distribution of the numerous superficial lymphatics of the dorsum of the hand. Provided by: J.P. Belgrado and A. Coulomb – Anatomy of the lymphatics collectors related to carpal tunnel surgery - Ethical Committee authorization number CHU Hôpital Erasme TFE_201812_228.

of the valves is essential for these mechanisms to run efficiently[21].

## Lymphatics in the Astronauts

The effect of microgravity induced by prolonged bed rest in comatose patients[22] or a stay in space[23], significantly modifies the body's distribution of fluids, both intra- and extravascular. Fluids are transferred from the extremities to the central regions of the body and to the head. This leads to an increase in filtration and, therefore, in the production of lymph, which must be evacuated from these areas.

As far as the edematous tissues, the dermis, and subcutaneous space are concerned, the number of lymphatic collectors is very high at the extremities and rapidly reduces towards the root of the limb, where they group together in a very narrow bundle (Figure 1 and Figure 2). The purpose of this very particular arrangement, resembling an inverted tree structure, is to allow the lymphatic function to "bring up" from the extremities the fluids and macromolecules which have "dripped" throughout the day while in an upright position.

**Figure 2.** Superficial lymphatic collectors of the plantar sole and distal lower limb. Anatomical specimen produced using 19th- and 20th-century mercury techniques. Source: Museum of Anatomy of the Department of Functional Anatomy and Embryology - Université Libre de Bruxelles. Dir. Prof. V. Feipel; Provided by: J.P. Belgrado.

The thighs and arms, conversely, do not have a network of collectors as numerous and dispersed as those in the extremities because, under normal gravity, these areas do not need to drain large quantities of fluid.

In space, fluids from the limbs are concentrated in the trunk and the roots of the limbs. This redistribution of the fluid results, on the one hand, in the dehydration of the extremities and, on the other, in fluid accumulation at the roots of the limbs. To reverse these fluid transfer mechanisms when humans are in space, we need to actively mobilize some of the fluids from the roots of the limbs towards the extremities[10].

Recently, a device[24] with this aim was successfully tested on lymphoedemas. By reversing its contraction sequence, this device, consisting of a lightweight dynamic sleeve equipped with a microcontroller and miniature motors, could help astronauts to distribute fluids more effectively. This dynamic sleeve is very light, easy to put on, and does not hinder movement, allowing the wearer to remain active on other tasks, while its very low energy consumption makes it compatible with the requirements of space missions[24].

Among the many physiological effects caused by these fluid transfers, there is an increase in cerebral blood flow[22], an increase in pressure in the subclavian vein, and turgidity of the jugular vein induced by an elevation of transmural venous pressure. This rise in intravenous pressure increases the resistance to the opening of the valves at the junctions between lymphatic collectors and veins (Figure 3). Although the boluses of lymph that must flow into the bloodstream at this point are not stopped, they are somewhat impeded.

Furthermore, as gravity no longer exerts the "weight effect" on the boluses of lymph accumulated vertically above the lympho-venous junction (Figure 4), the weight of the bolus, which contributes to the opening of the lympho-venous valve, is no longer effective. The neuromuscular apparatus of terminal lymphatics is hence over-solicited, even though it is not designed for such powerful continuous activity. The above phenomena contribute to both producing more lymph and slowing down its drainage. Natural compensations, such as decreased lymph production, linked to the progressive reduction in circulating fluids during a space mission, can partially lower the lymph drainage requirement. However, if the LS is not supported, a more or less significant edema in the tissues will gradually take form. The moon face, headaches, and major disorders such as visual impairment associated with the compression of the optic nerve, reported by astronauts[25] are an illustration of this pathophysiological process.

Genetics could also play a main role in the lymphatic response to microgravity. Lymphatic malfunctions, lymphatic malformations, and lymphedema can all be caused by genetic mutations in specific genes[26-28]. Although genetic mutations could not result in clinical pathologies in normal conditions, their effects may arise in stressful conditions such as microgravity[29]. Thus, genetic testing should be considered a standard procedure in space programs to check predisposition to lymphatic symptoms, all in the scope of personalized medical diagnosis and treatments[29,30]. Moreover, our current knowledge of the genetic etiology of lymphedema and lymphatic malformations is still lacking, and as such, new research in space programs could help unravel new mechanisms for lymphedema pathogenesis and lymphatic function.

**Figure 3.** Superficial lymphatic collectors of the scalp, head, and neck. Anatomical specimen produced using 19th- and 20th-century mercury techniques. Source: Museum of Anatomy of the Department of Functional Anatomy - Université Libre de Bruxelles. Dir. Prof. V. Feipel; Provided by: J.P. Belgrado.

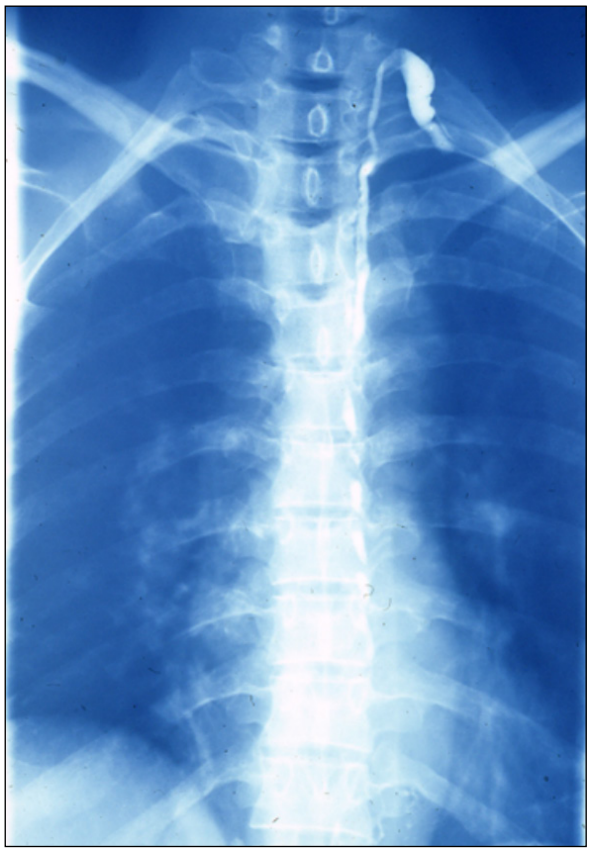

**Figure 4.** Thoracic duct observed with Xray lipiodol lymphography on leaving men in standing position. Provided by: J.P. Belgrado and J.D. Picard.

## Lymphofluoroscopy to Study the Behaviour of Superficial Lymphatic Collectors in Microgravity

Lymphofluoroscopy is a dynamic, minimally invasive, and repeatable examination that enables us to observe in real-time the passage of boluses of lymph made fluorescent by the intradermal injection of a small, highly diluted quantity of a vital dye: indocyanine green (ICG)[31,32].

After injecting ICG into the scalp, we can study the lymphatic drainage of the face by analyzing the dynamic behavior of the boluses of lymph. From the injection site, the fluorescent boluses of lymph pass through the superficial collectors of the face to reach the lymph nodes at the base of the neck (Figure 5), the same nodes that receive lymph from the endocranium and must empty into the jugular-subclavian junction, which in astronauts is under excessive pressure. Comparison in different positions (for example, vertical *vs.* tilted at -15°) of parameters such as transit time, bolus passage frequency, and fluorescence impregnation times of the lymph nodes at the base of the neck, among others, reflects the lymphatic load but also its drainage capacities.

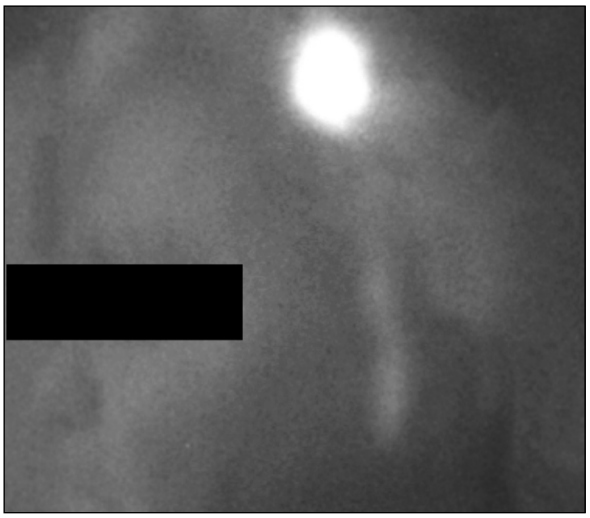

**Figure 5.** Superficial lymphatic collectors drain the parietal scalp *via* the preauricular lateral ways. Provided by: J.P. Belgrado and L. Vandermeeren.

## Conclusions

Long-duration space missions will not be possible without better integration of the physiology and pathophysiology of prolonged lymphatic insufficiency, due to the risk of jeopardizing the safety of the astronauts and the missions themselves.

Lymphofluoroscopy is proving to be a major tool for studying the behavior of the LS in microgravity. The protocols currently being developed will provide the keys to gaining a better understanding of the LS' involvement in such conditions, detecting latent lymphatic insufficiencies in astronaut candidates, and setting up specific maneuvers to improve lymphatic drainage in astronauts during their extended stays in space.

### Conflict of Interest

The authors declare that they have no conflict of interests.

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### Informed Consent
Not applicable.

### Ethics Approval
Not applicable.

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### Availability of Data and Materials
All data and materials are within the text.

### Authors' Contributions
Conceptualization, JPB, and MB; Writing - Original Draft, JPB and GB; Writing - Review & Editing, JMD, VS, GMT, PC, and SC; Supervision, MB; Funding acquisition, MB. Each author approved the final version of the manuscript.

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