The Spleen in Spaceflight

Possible Contributions to Altered Hemostatic Physiology and Circulation in Microgravity

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BACKGROUND

Studies related to splenic physiology during spaceflight have focused on its immune function. However, the internal jugular deep vein thrombosis discovered during a recent space mission spotlighted that the circulatory and hemostatic physiology of spaceflight is not yet well understood and likely involve not only aspects of hemodynamics, but also the output of the reticuloendothelial system (RES), which effects homeostasis via RBC clearance, mediates platelet formation and storage, blood viscosity, and thrombotic functions. On Earth, the spleen plays an active role in the RES and hemostatic physiology. What role might the spleen play in circulation hemostatic physiology during spaceflight and what alterations in its function should be expected in the microgravity environment?

RESEARCH OBJECTIVES

In reviewing the literature to date we sought to understand:

- Splenic effects on RBC clearance, anemia, and hemostasis
- Splenic and splanchnic contributions to arterial and venous blood storage
- How splenic and splanchnic physiology may alter in microgravity

The Spleen: Two Environments, Many Functions (and Dysfunctions)

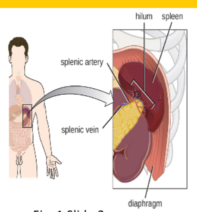


Fig. 1 Slide 2

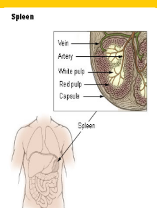


Fig. 2 Slide 2

Fig. 3 Slide 8

The spleen is the largest organ in the reticuloendothelial system and the second-largest immune organ in the human body

- Terrestrially, the spleen filters blood, stores blood products, produces antibodies, and can influence blood volume. It stores RNA-containing whole blood cells, leukocytes, reticulated platelets and reticulocyte RBCs
- Here, we focus on how the spleen might function as an unexplored, but important, element of the vascular system in human spaceflight, asking: How might the spleen be implicated in the incidence of venous thrombosis, the development of spaceflight anemia, the development and resolution of orthostasis, and the adaptive physiologic response to rostral fluid shift?

Nominal Function in 1g

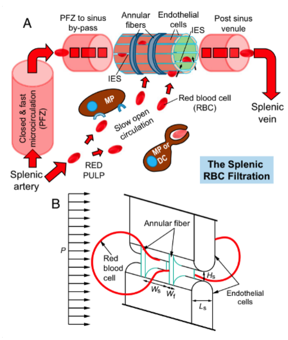


Figure 4: Slide 4

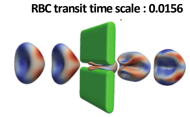


Figure 5: Slide 4

- ➢ Splanchnic veins hold 20–25% of total circulating blood volume
- ➢ Splanchnic organs receive ~25–30% of the cardiac output
- ➢ 100 mL/min is shunted to the spleen, where the IES filters out non-standard-shaped RBCs

Abnormal Function in Microgravity

Figure 6: Slide 4

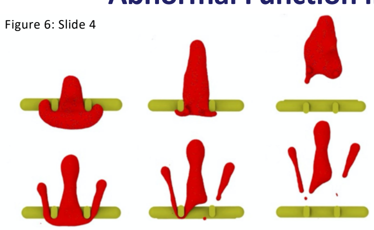
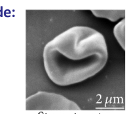


Fig. 7 Slide 3

In Microgravity RBCs Exhibit Altered Behavior ⟶ **More diverse morphology, increased fragility & vulnerability to removal by spleen**

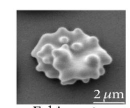
Cytoskeletal instability & splenic alterations of the RBC due to microgravity somewhat mirror spherocytosis in that they may include:

- ★ Loss of biconcavity & roughness
- ★ Decreased surface: vol ratio
- ★ RBCs take on a larger range of sizes
- ★ Decreased production
- ★ Selective hemolysis/neocytolysis
- ★ Altered consumption of the cell resources & morphology



Stomatocytes

Fig.8 Slide 3



Echinocytes

Fig. 9 Slide 3

Discussion and Considerations

Results from this literature review support the hypothesis that splenic function (and dysfunction) may affect on hemostatic physiology and circulation in microgravity

Possible mechanisms include:

- ★ Altered mechanical properties of RBCs leading to altered RBC longevity and subsequent:
  - Decreased RBC mass and RBC survival
    - Both are consistent laboratory findings since the Gemini missions
- ★ Acutely (in early exposure to microgravity) increased blood HCT
- ★ Chronically, as plasma volume drops, stored platelet release leads to increased risk of thrombogenesis
- ★ Development & resolution of nausea during acute space adaptation
- ★ Development & resolution of orthostatic hypotension status post return from microgravity

Understanding the role of the spleen in pre-flight, in-flight & post-flight patient management:

- ★ In taking a patient history, be aware of unexplained anemia and off-nominal RBC laboratory values including RBC indices and RBC mass
- ★ Using proactive surveillance to develop a clear, real-time picture of physiologic changes could help determine when and what countermeasures to employ now and in the future

Take-home from this review:

The splenic contribution towards hematologic function in microgravity is largely unknown, may be significant, and warrants further study in situ and in simulation.

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Splenic Physiology: 1G

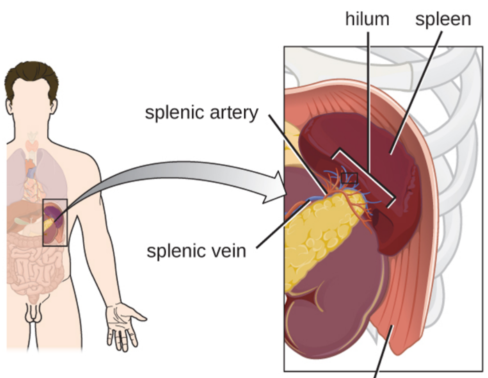


Figure 1: Structure of and location of the spleen in human body. Courtesy of Wikimedia Commons.

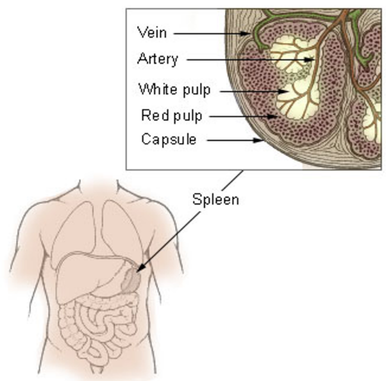


Figure 2: Cross-section of spleen showing white and red pulp and vascular structure. Courtesy of Wikimedia Commons

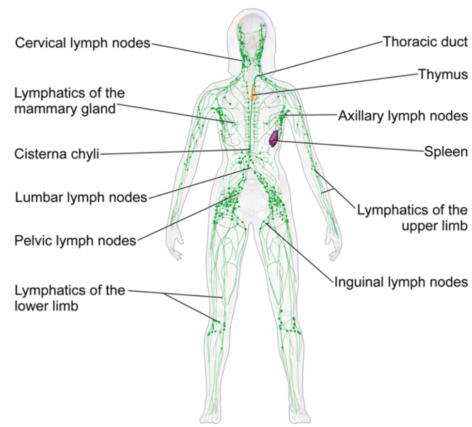


Fig 11. Organs and circulation of the immune system. Courtesy of Wikimedia Commons/WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010

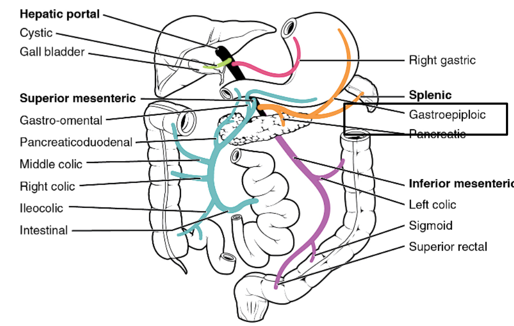


Fig 12. Hepatic Portal Vein System wth splenic circulation. Courtesy of Wikimedia Commons/Anatomy & Physiology, Connexions Web site

Basic Anatomy & Spaceflight-Significant Functions

Largest Reticuloendothelial System organ ❍ 2nd Largest Lymphoid Organ ❍ Located Between 9th and 11th ribs (Fig.1) ❍ Weights on average 150 gm, depending on BMI & gender (Sprogøe-Jakobsen, 1997)

Splanchnic Blood Capacitance

- ❍ Splanchnic circulation encompasses the vasculature of the stomach, intestine, liver, pancreas, and spleen. These organs constitute 10% of body weight but contain 25% of the total blood volume (Noskov 2014)
- ❍ Basal blood flow to the splanchnic region far exceeds non-exercising metabolic requirement. This area therefore serves as the body's main blood capacitance system/functional blood reservoir
- ❍ Nearly two thirds of the splanchnic blood (i.e. > 800 ml) can be auto-transfused into the systemic circulation within seconds when demand increases

Splenic RBC Filtration

- ❍ In terms of cardiac output, the spleen only receives ~100 ml, as compared to the liver and intestines, which each receive ~300 and 400 ml of ejected blood volume, respectively
- ❍ However, the hematocrit of the blood within the spleen often approaches 75% secondary to significant RBC concentration as it filters 10% of that blood through tiny interendothelial slits (IES)

Platelet Storage

- ❍ Stores senescent platelets for later removal. In conditions such as hemorrhage and extensive burns, may release these platelets into circulation (Sahler 2011)

Lymphoid System

- ❍ Plays a significant role in immune function with high lymphatic circulation. While immunology is a significant concern for space flight, the clinical ramifications of the spleen's role are not well understood.

Spleen & Splanchnic Circulation in Spaceflight: Potential Contributions to Spaceflight Anemia

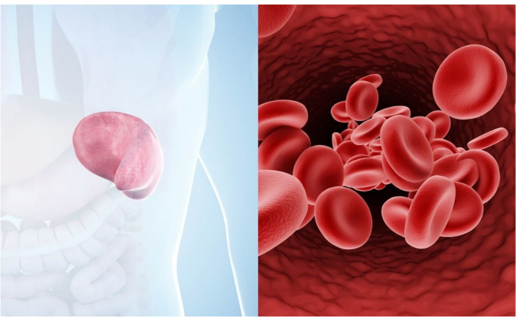


Figure 7: Normal RBC in 1 g. Courtesy of Wikimedia Commons.

Possible model of pathophysiology for spaceflight anemia

The literature reports that in space RBC cytoskeletal structure alters → Rounder RBCs → Abnormal RBC morphology → Damage during RBC passage through splenic IES → Premature aging → Early removal by spleen → Persistent anemia

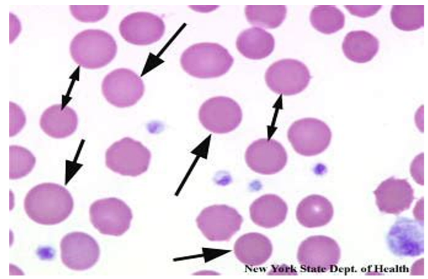
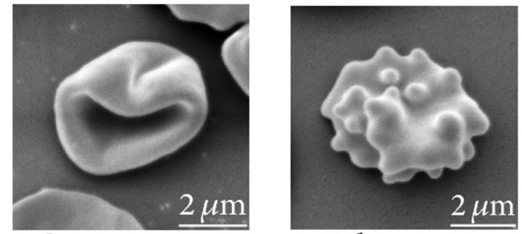


Fig 15: RBC under microscopy, arrows denoting spherocytes. From NY Health Dept.



Figures 8 & 9: Other types of aberrant RBC morphology seen in the context of decreased cytoskeletal control and ATP storage

Normal RBC in IG

- ~6 µm in size
- ~120-day lifespan
- Lack nuclei AND mitochondria
- Biconcave, highly flexible, disk-like
- Notable "Roughness" surface feature

RBC Morphology in Microgravity is Similar to Spherocytosis and Accelerated RBC aging

As RBCs age → loss of biconcavity & roughness → Decreased surface: volume ratio → rounder cell

Rounder RBCs in microgravity may mimic senescence

Multiple in vitro studies suggest that microgravity contributes to abnormal morphology of RBCs. One consistently cited mechanism is alterations to cytoskeleton membrane-skeleton properties. Others are:

- ★ **Spaceflight-induced oxidative stress** and d**ecreased** production of RBCs (Udden 1995)
  - Reduced erythropoietin levels (DeSanto 2005)
- ★ **Selective Hemolysis/Neocytolysis** (Dinarelli 2018)
  - Of newly formed Red cell mass
  - Of existing RBCs
- ★ **Increased Oxidative Stress** (Rizzo 2012) & Altered Metabolic Patterns (Dinarelli 2018)
  - Rate of consumption of the cell resources balloons
- ★ **Altered morphology** & "distinctive morphological patterns of aging" (Ivanova 2011)
  - Increased echinocytes, stomatocytes and knizocytes

***Any and all of these factors* could lead to increased RBC removal from circulation and contribute to the observed, persistent phenomenon of spaceflight anemia**

Drilling Down:
RBC Filtration in 1G VS Microgravity

Biomechanics of red blood cells in human spleen and consequences for physiology and disease

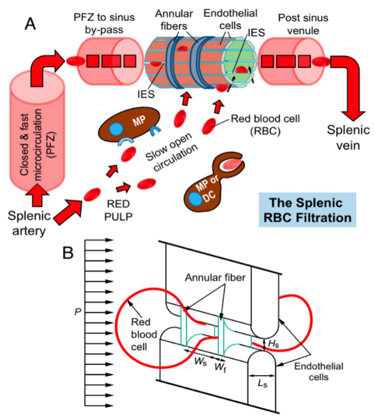


Figure 4: Depicting RBC interaction with IES, which filers cells with abnormal morphology or fragility. Images courtesy of Dr. Ming Dao, co-author. Pivkin (2016)

RBC filtration time scale : 0.0156 sec

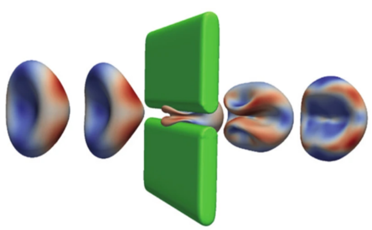


Fig 5: Model of an RBC passing through an IES. This is how the IES bounds RBC population morphology. Dao 2021.

IES Filtration Determines the RBC Population in Circulation

Nominal Case: Deformation and Return to Circulation or Sequestration

★ As blood flows through the spleen, about 10 percent of the red blood cells are diverted through the interendothelial slits (IES).

★ This forms a mechanism for microfiltration & extraction

- Filter dimensions are roughly 1.2 micrometers in height, 4 micrometers in width, and 1.9 micrometers in depth.
- The RBC passes through this IES microfilter in the human spleen at a constant pressure gradient of 0.64 Pa/µm.
- An RBC is only allowed *a very small change* in total surface area from its undeformed value of 122 µm 2: up to 7%
  - Deformity beyond these constraints risks sequestration and removal

Off-Nominal Case: Abnormal Morphology & IES pressure gradients → Increased Removal

★ Pressure gradients across the IES are likely off nominal in space

- Higher than in 1g in the acute phase of spaceflight
- Lower than in 1g after space traveler has diuresed their PV

★ Atypical morphology (similar to spherocytic RBCs) with increased fragility due to abnormalities of the components of the RBC membrane cytoskeleton risk further deformity in the IES & removal from circulation

The literature suggests that for these reasons in spaceflight, RBC risk for removal by the IES may increase: possibly dramatically

On Earth, splenic interendothelial slit (IES) bound the biophysical limits of RBC viability.
This should also be true in space.

Significant Question: How are bounding parameters changing and effecting hemostatic physiology in space?

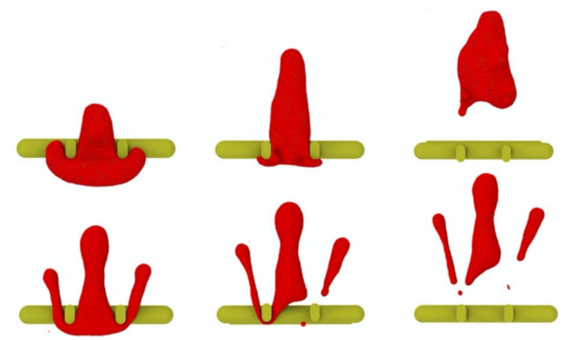


Figure 6: Top row depicts RBC with compromised cytoskeleton, which passes through the IES misshapen but intact. Bottom Row depicts further degraded RBC which is unable pass through IES without hemolyzing. Images courtesy of Ming Dao, co-author. Pivkin 2016.

Spleen & Splanchnic Circulation in Spaceflight: Potential Contributions to Thrombogenesis

Effects Mediated by the Spleen Vary By Time and Blood Volume

1. In periods of relatively low pressure, may contribute to thrombogenesis
2. Under high blood pressure, may prematurely remove RBCs (Filtration)
3. Possible contribution to spaceflight anemia (Spaceflight Anemia)

Spaceflight Splanchnic Capacitance: Acute Phase

★ **Upon arrival in microgravity,** cardiac output is acutely increased by ~30%

★ Additional cardiac output & lower extremity fluid is then diverted into splanchnic circulation

★ Per Johnson (1977) hypersplenism may start very early in the mission when the blood volume is shunted from the lower extremities into the torso and upper extremities

★ This fluid shift can also be associated with the increased portal pressure and/or decreased portal flow

★ *All of this is consistent* with the 2 or 3 days of nausea and loss of appetite reported by susceptible crewmembers on arrival to microgravity

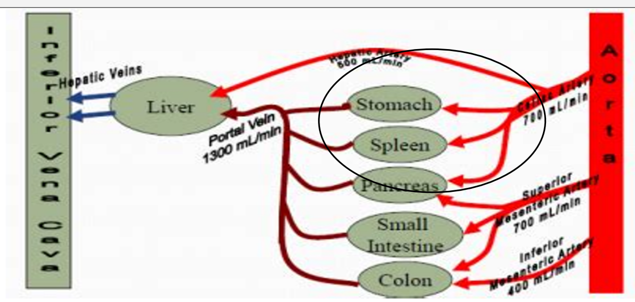


Fig 13:
The low pressure, high capacitance system that is splanchnic circulation adapts to microgravity in important ways, acutely and chronically

Parameter	Horizontal position without administration of a diuretic	AOP: without administration of a diuretic	AOP: after administration of a diuretic	Parameter	Horizontal position without administration of a diuretic	AOP: without administration of a diuretic	AOP: after administration of a diuretic
Liver (left lobe), mm	77 ± 3	83 ± 2*	79 ± 3	Left vein of liver, mm	5.7 ± 0.2	7.6 ± 0.1*	5.6 ± 0.3
Pancreas (tail), mm	20 ± 1	26 ± 2*	27 ± 2*	Splenic vein, mm	7.4 ± 0.2	10.0 ± 0.1*	8.9 ± 0.2
Spleen, mm	31 ± 3	47 ± 4*	45 ± 4*	Superior mesenteric vein, mm	8.3 ± 0.1	11.2 ± 0.2*	10.5 ± 0.3
Gallbladder, mm	23 ± 1	15 ± 1*	24 ± 1	Gallbladder volume, ml	19 ± 1.4	14 ± 0.4*	18 ± 0.4
Common bile duct, mm	1.9 ± 0.2	6.0 ± 0.2*	2.0 ± 0.2	Stomach liquid volume, ml	22 ± 2	73 ± 3*	29 ± 4
Common portal vein, mm	12.8 ± 0.4	13.1 ± 0.5	13.5 ± 0.3	Duodenum lumen, mm	25 ± 3	44 ± 4*	54 ± 2*
Central vein of liver, mm	7.4 ± 0.1	9.0 ± 0.1*	7.3 ± 0.1	Ileum lumen, mm	33 ± 1	44 ± 5*	52 ± 2*

* A significant change compared to the horizontal position ($p < 0.05$).

Figure 14: Engorgement of spleen and splenic vein seen in microgravity analog (Head-Down Tilt Bed Rest Study). From Noskov 2007.

Splanchnic Capacitance: Chronic Phase

★ During prolonged spaceflight, Plasma Volume (PV) contracts from dehydration and diuresis

★ This decreases the volume of blood held in splanchnic circulation and results in lower pressure exerted on the spleen

★ Remember: Part of the spleen's normal function is to release platelets in response to low circulating blood volume

★ As a stress response to hemorrhage, this is life-saving

★ *As a response to PV loss in microgravity, the spleen's release of platelets may increase the potential for thrombogenesis as long as PV is relatively low*

Predicting Impact: Towards a Model of Splenic & Splanchnic System Dynamics

Using Computational Simulations to Quantify the Biophysical Behavior of the Splenic RES

- ★ Examples of how computational modeling is allowing us to achieve greater understanding of organ systems and circulation in microgravity include:
  - IES-level models by Li (2018) and Pivkin (2017)
    - Visualizes the size of the slits and the amount of pressure on the cells as they flow through the spleen using computational input
  - Sucosky's (2021) model of the hemodynamics of blood and turbulence in vasculature in microgravity
  - Lan's (2000) model of resistance and capacitance in vascular beds
- ★ The challenge
  - To combine approaches like these to create an IES-to-splanchnic vein computational model of the spleen
    - One that demonstrates how the flow-dependent characteristics of RBC filtration alter with blood pressure, splanchnic capacitance, and RBC morphology, and time spent in microgravity

The Goal: To create a model that can be validated in 1g in vitro and in vivo simulations, then verified using laboratory tests and ultrasound, both of which are currently available on the ISS.

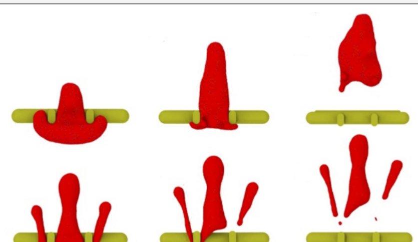


FIgure 6: Model of IES filtration of an RBC Courtesy of Dr. Ming Dao

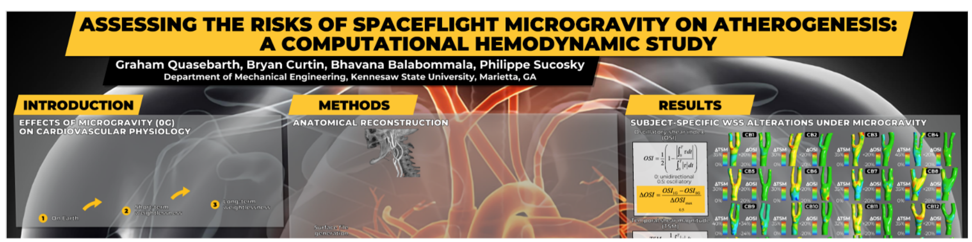


Fig. 10: Computational modeling of vascular function and dysfunction in spaceflight may provide the critical pathway for predicting the sequalae of organ function, which we can then test for and plan for during actual spaceflight. From Sucosky (2021).

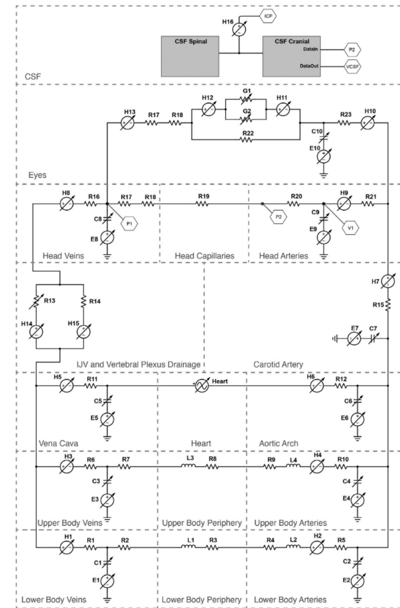
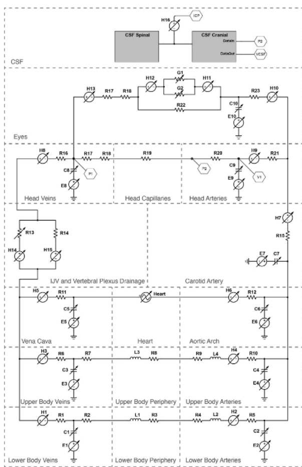


FIgure 16: Vascular modeling using circuitry to describe resistance and capacitance of different vascular beds. Used with permission and gratitude. Courtesy of Mimi Lan and Jay Buckey (2020)

Modeling Considerations for Understanding The Spleen's Role in Microgravity Physiology

Current State: We learn about organ function in space post-hoc, when a problem is picked up

Desired State: Using pre-mission modeling at the vascular system, organ level, cortical tissue level, and cellular levels; testing predictions in-mission, and using results to refine the model post-mission. Iterate until the models are right



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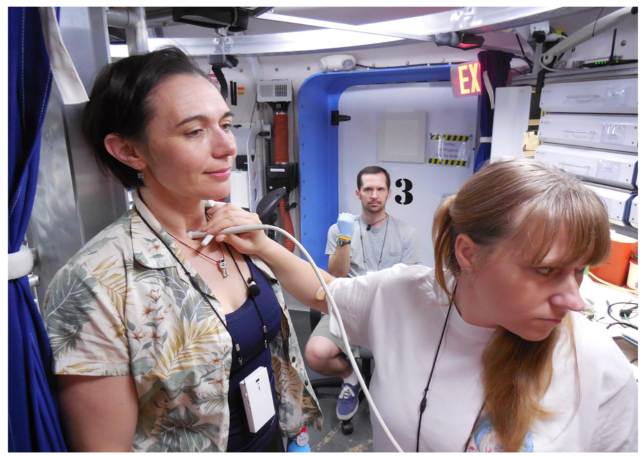

Simulated Astronauts Linda Roerborn-Rodriguez and Sheyna Gifford perform ultrasounds in the Huma Exploration and Research (HERA) space analog (2015)

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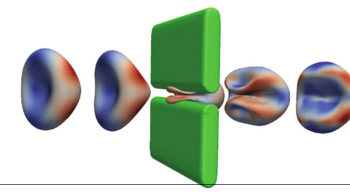


What Splenic Functions Can We Not Yet Model?

★ IES microfiltration; deformity and damage to the RBC

★ Pressure in the splenic artery and vein

★ Microgravity-induced changes in immune function

- ▪ Attempts to reproduce these effects in animal models have not been successful (Pecaut, 1999).

What Splenic Functions in Microgravity Would We Like to Model?

★ Microgravity-induced changes in splenic function as they vary over the course of the mission, including:

- Engorgement, altered immune function, release of stored platelets, hemoconcentration, IES filtration.

What Splenic Functions Can We Currently Model?

★ Acute phase splenic engorgement

- ▪ Can simulate in 1g using head-down tilt table studies
- ▪ Resolves with induction of volume depletion (administration of diuretics) Noskov et al (2007, Oct 2013, Dec 2013).

★ Desensitization of α1-, α2-, and β2-adrenergic receptors

- Upon return from medium-to-long-term space missions, flyers often demonstrate autonomic dysregulation
  - ▪ possibly due to desensitization of α1-, α2-, and β2-adrenergic receptors in the arterial supply of the preportal splanchnic organs, contributing to excess splanchnic capacitance, orthostatic hypotension, intolerance for acute positional changes post-flight
- Earth models for this are patients with spinal cord injuries, who suffer from this effect chronically

Future Considerations: Splenic Ultrasound

Should Splenic Imaging Be Included in the Standard NASA Abdominal Ultrasound Protocol?

★ **In Typical Earth-based medicine:**

- Spleen size is an integral part of abdominal ultrasonography (US) because both abnormally large and small spleens can be indicative of a condition (Chow, 2016).
- Normal values have been established based on sex, height, BMI
- The scan can be technically challenging as the spleen has a variable 3-dimensional (3D) shape
  - Volume, therefore, not easily calculated.
  - Volumetric measurements more accurately obtained by computed tomography (CT), magnetic resonance (MRI) , or 3D-US
  - BUT Repeated measurements appear highly consistent on CT and on sonography (Bezerra et al 2005, Lamb et al 2002), therefore

In space: Technical challenges may arise as spleen will not always be in the same location, but multiple simple US measurements of spleen length may be a practical surrogate to estimate of spleen size.

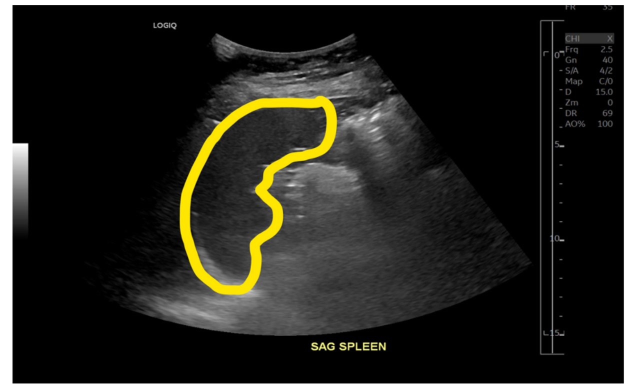
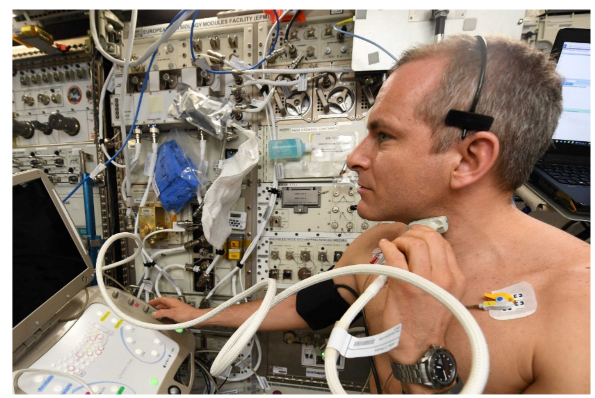


Fig 3: Sagittal View of the spleen on ultrasound in 1 g. Courtesy of David Lerner



Astronaut David David Saint-Jacques uses ultrasound on the ISS.
Credit: Canadian Space Agency/NASA

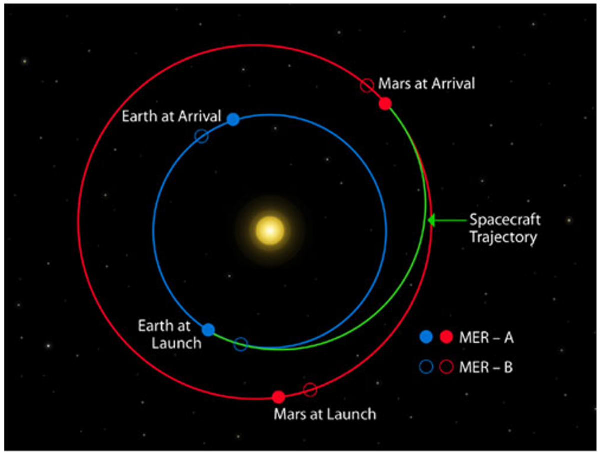
Future Considerations: Rationale for Splenic Ultrasound

The current pre-Flight NASA abdominal US protocol does not include the spleen - should it?

Pre-flight Assessment via US or MR:

★ Absence of splenomegaly is a requirement for peripheral blood stem cell donation (Noskov 2007 & 2013, Fink 2012, Johnson 1977) and as a requirement for participation in contact sports after infectious mononucleosis to reduce risk of splenic rupture

★ **Imaging provides practical means of establishing baseline spleen dimensions**



This is a representation of transit trajectory from Earth to Mars, projected on planetary orbits. Credit: NASA.

Post-flight Assessment:

★ Similar to early phases, surveillance provides two-fold benefit.

- Firstly to use proactively prevent development of abnormal physiologic state, until fluid balance returns to homeostasis
- Secondly, greater understanding of physiologic changes upon return to nominal 1G environment across multiple subjects.

In-flight Assessment:

In Noskov's 2007 head-down tilt table experiments, sonography showed that simulated microgravity environment caused increases in:

- The diameters of hepatic, portal, and splenic veins, the sizes of the liver, pancreas, and spleen; and
- The thicknesses of the stomach, intestine, and gallbladder walls compared to the values in a horizontal position."

★ Technology currently onboard the ISS could provide insight into the actual response of the spleen and splanchnic vascular response to microgravity in real time.

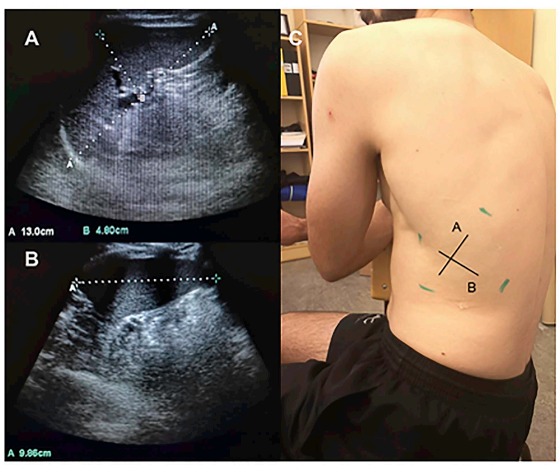
★ Such surveillance could be used evaluate and initiate proactive countermeasures prior to development of abnormal pathology, such as a hepatic and portal thrombogenesis, particularly during longer duration missions.

From the Literature: Considerations for In-Flight Intervention

In-Flight Intervention: Near Term

★ Unresolved Space Adaptation Syndrome (SAS)
- Nausea secondary to visual-vestibular system imbalance should resolve rapidly due to habituation
- Nausea due to engorgement of splanchnic vessels and gastric compression should resolve as flyer's PV drops:
  - Loss & redistribution of intravascular volume → decreased splanchnic capacitance & decreased pressure on spleen
- If nausea fails to resolve in past first week, splenic and/or splanchnic pathology should be included in the differential diagnosis.

Image to the Right: This sequence of ultrasound images shows how tri-axial measurements of the spleen can be used to make reliable volume calculations. The spleen views shown here are maximal length and thickness **(A)** and spleen width **(B).** These were taken by scanning the dorsal/posteriorlateral side of the body **(C).** Images are courtesy of Pontus Holmström and Erika Schagatay, Mid Sweden University, Östersund, Sweden. 2020.



In-Flight Intervention: Long Term

★ The spleen is implicated in potentially relevant vaso-occlusive and pro-thrombotic processes:
- Potential pathways include
  - Biochemical: Reduced nitric oxide bioavailability, provoking endothelial dysfunction and altered vasodynamics
    - Subsequent pro-oxidant effects leading to vascular inflammation via endothelial damage, activation, and elevated oxidative stress
- Splenic engorgement & hypersplenia are associated with increased risk of thrombosis (Kamisasa 1979)
- Decreased splenic blood flow following circulating blood volume loss:
  - May induce release of platelet stores by the spleen → increased thrombosis/thrombogenesis

★ Is blood flow ever so low in that splenic functions are suppressed?
- If so, this may also increase risk for venous thrombosis
  - Incidence of thrombosis is known to increase post-splenectomy (Watters 2010, Lee 2015, Filippova 2020)

Literature Review Methodology & References

Literature Review Methodology:

- Published media with terms related to: "spleen", "hematology", "abdominal viscera", "vascular system" in true microgravity and spaceflight analogs were included
- In vivo and vitro experiments
- In human and animal models
- In English and Russian where translations were available
- Published between January 1958 and October 2021

Results included: Peer-reviewed scientific journal articles books, technical reports, and published conference proceedings.

These 192 results were hand-searched for relevance and supplemented with backward reference searches and citation mining of relevant information.

Final Result: 62 Articles Included In Review

References & Articles Reviewed for The Spleen in...

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