

Space Cardiovascular Pharmacology



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An astronaut in a white space suit is working on a satellite in orbit above Earth. The astronaut is holding a large, circular component of the satellite. The Earth's surface is visible in the background, showing blue oceans and white clouds. The text is overlaid on the left side of the image.

Context

***Spaceflights,
Microgravity and early
cardiovascular aging
Space pharmacology
challenges***

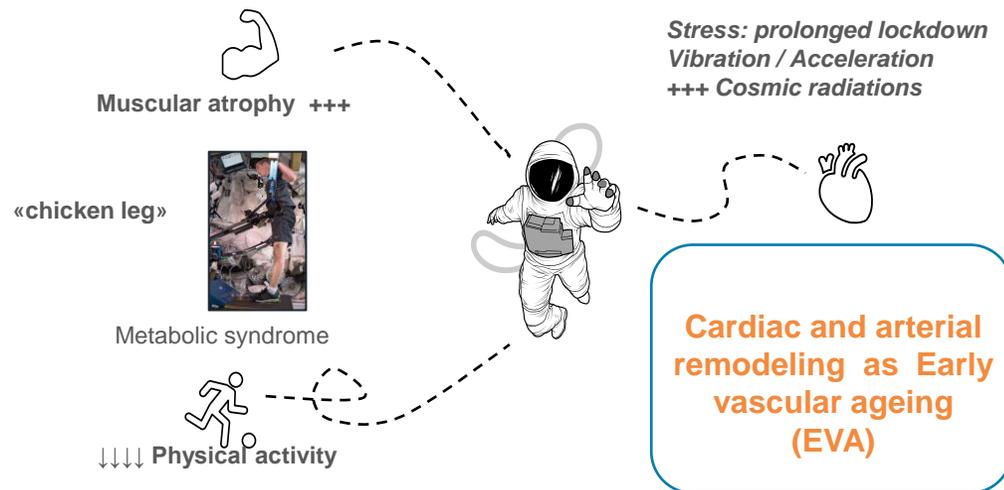
PK/PD studies in space

***Pharmacological
countermeasures***

Microgravity

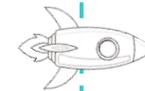
Cardiovascular deconditioning

Long term (> 6 months)



Forced Sedentary lifestyle

What is Early Vascular Ageing?



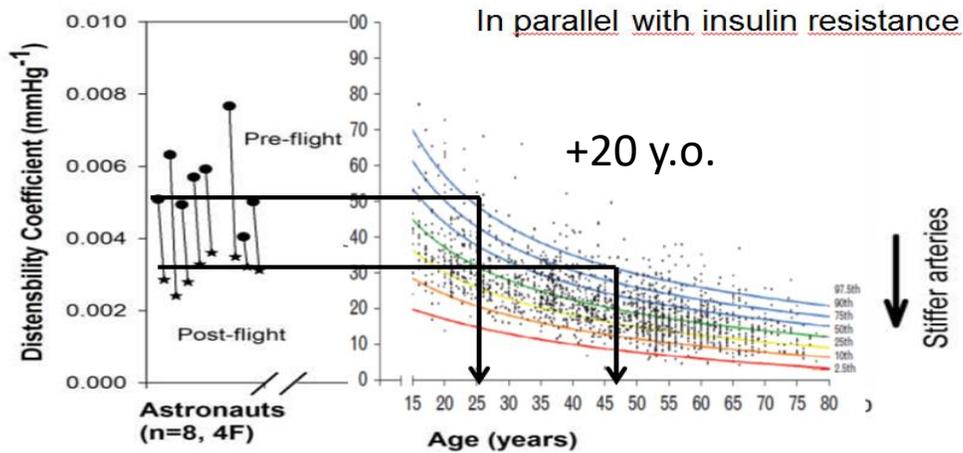
https://www.youtube.com/watch?v=7s0_Rkg_bRE

Animation by VasAgeNet

Microgravity

Early vascular ageing in space

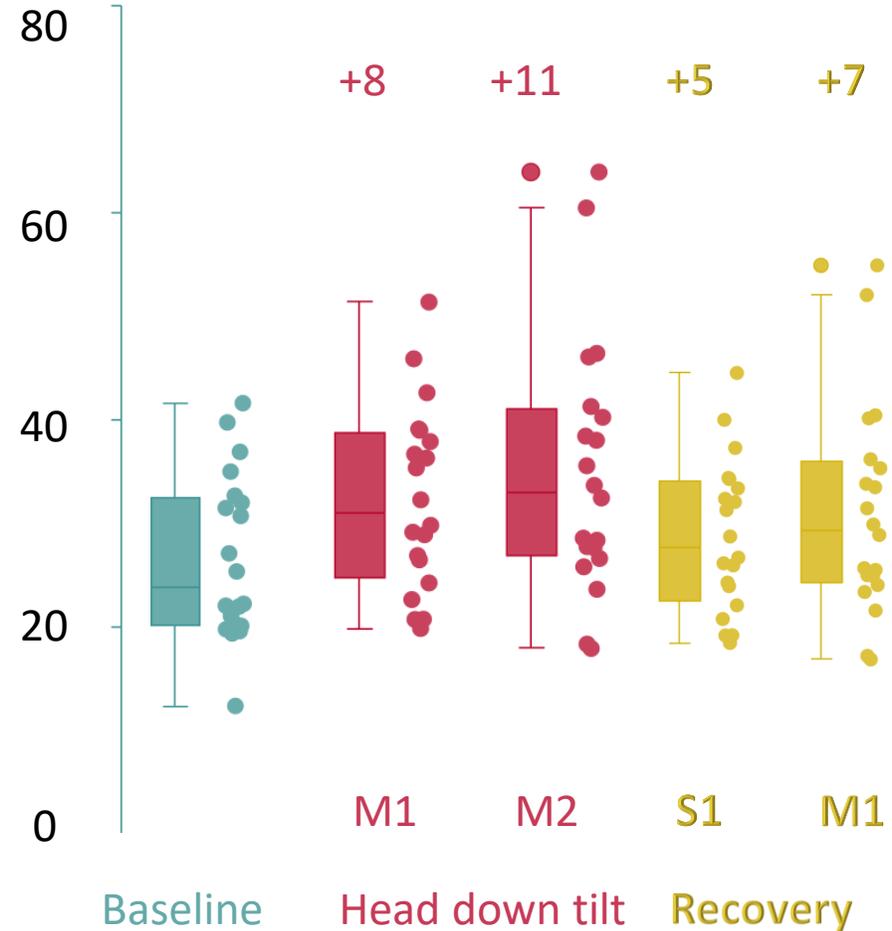
Effect of long-term spatial conditions on carotid distensibility



Arterial stiffness (pulse wave velocity or distensibility) are undisputed hallmarks of vascular ageing

Vascular age (years)

"Cocktail" head down tilt



Boutouyrie *et al*, submitted

Microgravity

Pharmacology in space

Why is it needed ?

- **Profound modification of body in space**
 - Composition and metabolism affecting drug pharmacokinetics and pharmacodynamics
- **No pharmacological countermeasures** yet proposed for space related health issues including early vascular ageing
- **“Older astronauts”** to be expected with potential health issues
- **Long term flights** → increased risk of disease to be managed

Why is it missing ?

- **Obstacles for Pharmacological studies**
 - Logistical and technical constraints of sample biologicals fluid
 - Difficulties of dosages
 - Analysis on board not feasible yet

STRATEGY

A detailed rendering of a SpaceX Dragon capsule in orbit above Earth. The capsule is white with blue accents and features the SpaceX logo and an American flag. The Earth's atmosphere is visible as a blue and white horizon, and a crescent moon is seen in the blackness of space in the background.

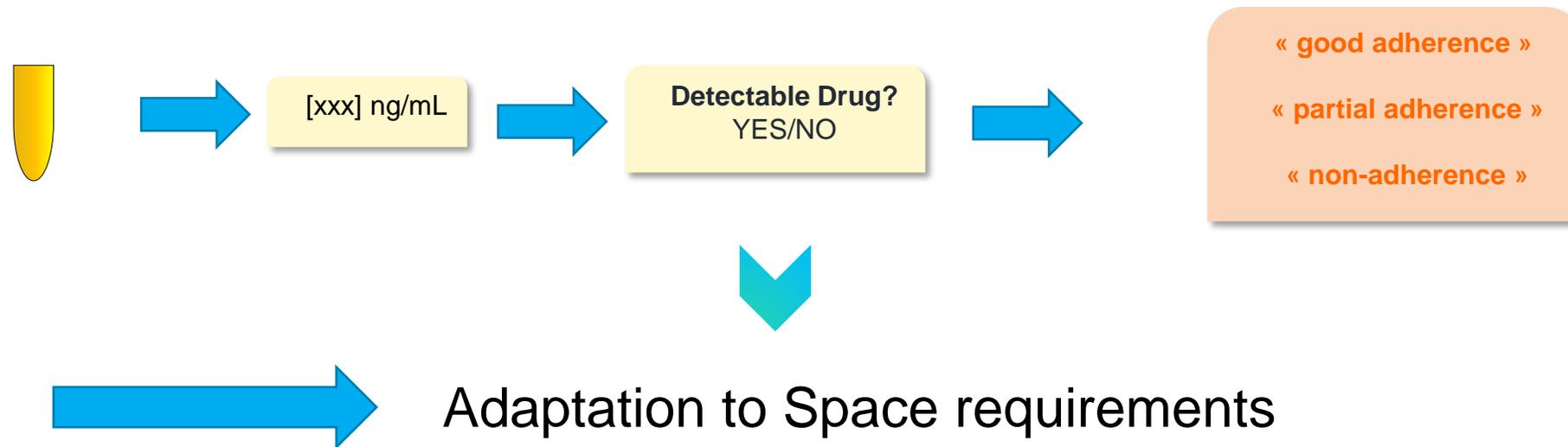
- **Development of new methodologies based on LCMS/MS for drug detection/dosage**
- **Define a strategy for pharmacological countermeasures**

Antihypertensive drugs dosage

Medical practice

Currently

Quantitative LC-MS/MS dosage of 24+ cardiovascular drugs, urine samples, adherence to antihypertensive medication, routine clinical practice at our laboratory

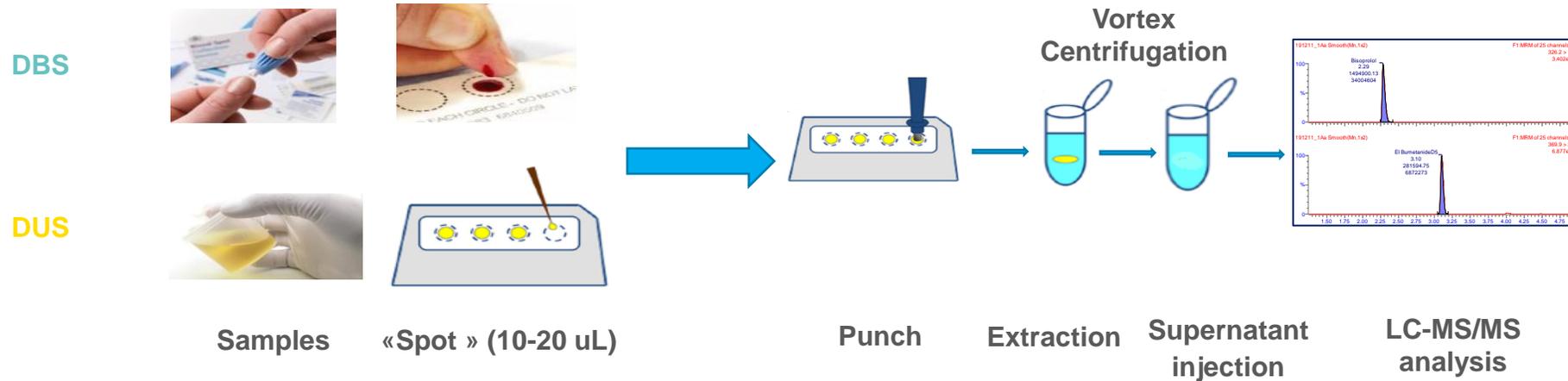


Hamdidouche et al. J. Hypertens, 2017
Kably et al, Curr Op Hyper, 2020

Drug dosage in Space

Developpement

Innovative dried matrix spot technique use (DUS, DBS)* applied to drug dosage, coupled with LC-MS/MS dosage could be the ideal methods for Space Pharmacology



- My Master's research : Validation of 5 cardiovascular drugs detections on Dried Urine spot (*paper in progress*)
- PhD to be started...

* DUS = Dried Urine Spot; DBS = Dried Blood Spot

Dried Matrix Spot

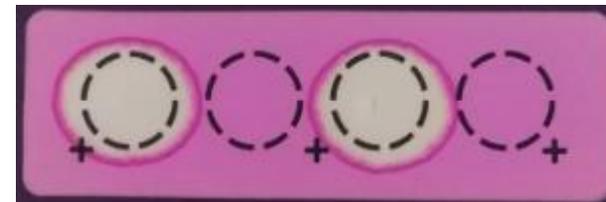
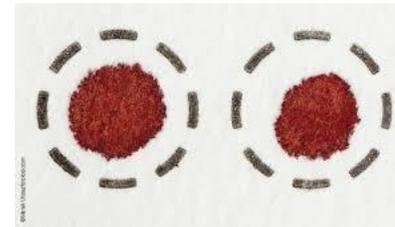
Characteristics

Advantages

- Easy and fast collection
- Not limited to drugs (infectious disease etc)
- Self-collection by non-professional health care
- Safe, lower risk of biohazard
- Minimal requirements for transport (< 3 grams/sample)
- Resistance to stress and conditions of storage
- Very small volume of biological fluids needed
- Apt to repeated biological fluid sampling
- Very low cost
- Applicable to extreme environments and remote areas

Limits

- Not all drugs are detectable (according to their chemical properties)
- Long development for each compound to detect





Pharmacology
studies

Research Platforms for Pharmacology studies

Self management of samples in isolation

Cardiovascular Monitoring and Pharmacology on Mars COSMOS

- Isolation / confinement
- Hostile environment

Mars Desert Research Station (MDRS)



Dec 2021

Microfluidics in microgravity

Pharmacology Space Kit PSK

- Microgravity (lunar/martian gravity)
- Hypergravity

Parabolic flight



Mars 2022

Changes in drug metabolism induced by microgravity

Pharmacology Space Kit PSK

- Weightlessness simulation
- Inactivity/unloading

Bed Rest



2022

Mars Desert Research Station

Presentation

- 2 weeks Simulation in **December 2021**
- **The Trans-Atlantic Mars Society MDRS Team will conduct our project :**

Crew Commander : James Burk
Executive Officer and Safety Officer : Aline Decadi
Crew Engineer : Julien Villa-Massone

Crew Scientist : Frederick Bigrat
GreenHab Officer : Cécile Renaud
Crew Geologist : Guillaume Thirion



At MDRS

- COSMOS - PASKAL-Caffeine
- A screening study of caffeine and metabolites in blood and urine

Why caffeine ?



COSMOS - PASKAL-Caffeine

A screening study of caffeine and metabolites in blood and urine

Why caffeine ?

- Caffeine is a natural psychoactive substance naturally present in coffee → avoids regulatory issues
- Spatial environment may alter the drug metabolism and its response (Putchaj 1991, Eyal S et al 2019)
- To date, no terrestrial simulation model has yet been validated for the PK/PD study under space conditions (Kast J et al, 2017; Blue RS et al 2019)
- Cytochromes (CYPs) are critical enzymes for drug metabolism
- CYP1A2 is a well-known metabolic pathway involved in the elimination of common drugs (Lidocaine, Melatonin, Caffeine...) included in ISS medical KIT (Wotring VE 2015)

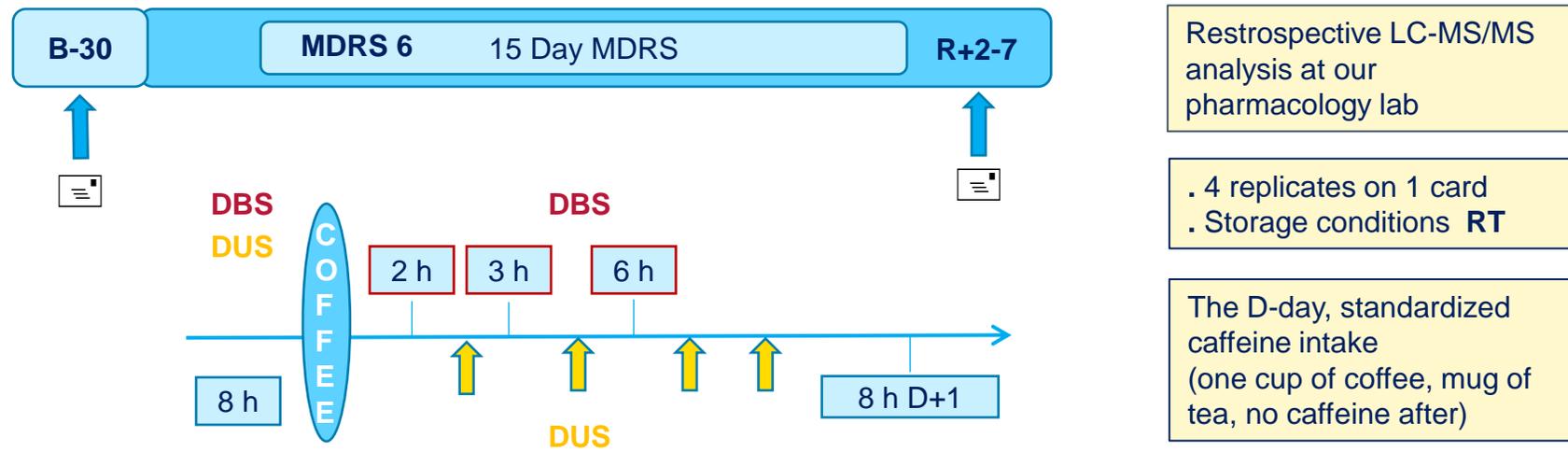
Objectives

- To evaluate the feasibility of blood/urine collection for DBS, DUS
- Propose a unique PK exploration using coffee as a probe
- To have a functional picture of a main metabolic pathway and its modifications during the study

COSMOS - PSK-Caffeine

A screening study of caffeine and metabolites in blood and urine

At MDRS



- Subjects: MDRS (Utah) team as a whole
- Training: The finger-prick test will be supervised by our team during the 1 day training at INSERM U970 (Paris, France)
- A video instruction will also be accessible for a self-instructive material and a effective training for collection of DBS/DUS

COSMOS - MAEVA

MArs Early Vascular Ageing monitoring

At MDRS

Hypothesis

- Aortic PWV increases during space flight, and will remain high after Mars landing and does not normalize after return

Proposition

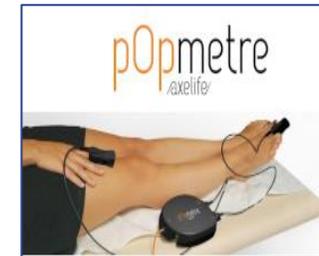
- A cardiovascular follow-up of the Mars analogue mission to all participants (PWV and blood pressure)

Material

- Assessed non-invasively by the pOpmètre® , connected weighing scale Withings®
- Advantages are simplicity, rapidity, feasibility, acceptability by patients, suitable to transport

Objectives

- To evaluate our procedure and test our material in isolation
- To evaluate the impact of extreme environment and confinement on PWV/EVA and vascular modifications during a Mars Analogue Mission
- PWV may serve for blood pressure estimation



https://www.youtube.com/watch?v=4aFnQ_0_bOI



Withings®

Why COSMOS and PSK projects are crucial for long-term Space missions?

Cardiovascular health is essential for astronauts for fulfilling missions and for their future life. Investment in manned Space missions require optimal drug safety for fully operational astronauts.

COSMOS and PSK will make possible:

- To test technologies and procedures of early vascular aging in extreme environment: pOpmetre® and the connected balance Withings® as health monitor
- To establish rigorous protocols for handling and storing human Martian biological samples before returning to “Earth” for analysis
- To test a unique smart support, multifunctional, easy to transport and economical : the dried matrix. Very simple “analogic and robust” methodologies not requiring IT resources. Final objective is to improve the comfort of Marsonauts/ Astronauts

MDRS/ Parabolic Flights / BED REST provide a unique research environment to validate new technologies and to define new control strategies

Thank you !



Email: audrey.derobertmeasure@etu.u-paris.fr