Lymphomics; improving the understanding of the anatomy of the lymphatic system and the direction and velocity of lymph flow

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To improve the knowledge and understanding of the (patho)physiology of lymph disorders
Main objective: the anatomy of the central lymph vessels, the velocity and direction of lymph flow and its influencers and thoracic duct outlet location and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spleen, lymphatic and reticuloendothelial system disorders
Study type	Observational invasive

Summary

ID

NL-OMON54295

Source
ToetsingOnline

Brief title
Lymphomics; improving the understanding of lymph

Condition

- Spleen, lymphatic and reticuloendothelial system disorders
- Blood and lymphatic system disorders congenital

Synonym
Lymph flow disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Anatomy, Lymph flow, Lymphatic system

Outcome measures

Primary outcome

Main study parameter/endpoint:

Anatomical measurements of both the thoracic duct and the cisterna chyli (conducted in the coronal plane on whichever MR sequence offers the best visualization of these structures). Measurements consist of the maximal diameter of the thoracic duct and the diameter at the level of the diaphragm, and the width and length of the cisterna chyli. Lymph flow velocity will determined by distance covered over time in cm/min. This will be calculated for both retroperitoneal lymph vessels and the thoracic duct. Thoracic duct outlet location and patency will be determined using contrast-enhanced ultrasound imaging of the left and right neck.

Other study parameters:

Patient characteristics such as: age, gender, body weight. Due to the effect of dietary intake on flow (specifically dietary fat intake), time since last meal, number of calories and fat content will be recorded and analyzed.

Secondary outcome

Secondary study parameters/endpoints:

Not applicable.

Study description

Background summary

Lymph is part of the fluid that is in the interstitium of the body. It circulates via the lymphatic vessels and is connected to the venous system, in particular the subclavian veins. Lymph contains lymphocytes and has a role in the immune system. Lymph from the liver and bowels is called chyle and contains a large amount of triglycerides and peptids, and this has an important function in feeding the body.
The knowledge of lymph is limited. The organ of lymph, consisting of vessels en nodes, seems to be a much forgotten or neglected one for the last decades. Knowledge of the embryology, etiology and anatomy as well as knowledge of lymph function and etiopathogenesis of lymphatic disorders is largely unknown and much is to be discovered yet. This goes especially for the (patho)physiology of the flow of lymph in the central lymph vessels.
Primary edema of a limb, ascites, chylothorax or leakage of lymph or chyle can be impairing for normal development, daily activities and quality of life. The cause can be found in a congenital anatomic or conducting disorder of the lymph. The types can be divided per cause (congenital or acquired) or per location (central or peripheral). In fetuses, a central conducting disorder can result in fetal hydrops and this can be lethal. Central lymph flow disorders may be acquired after (retroperitoneal or mediastinal) disease or surgery, due to extensive removal of lymph nodes or injury to the thoracic duct. If the lymph cannot flow into its mouth in the subclavian vein, it may leak in a more upstream level, either as chylothorax, chyloascites or lymphedema or even chylus leaking from the scrotum or vagina. Peripheral lymph flow abnormalities can result in edema of an extremity, which can be congenital (primary) or postoperative (mostly after lymphadenectomy for oncologic reasons).
It is not known how many people are impaired with lymph flow disorders, as many of these patients have unrecognized symptoms and remain without diagnosis. This goes especially for the patients with congenital central lymph flow disorders.
For instance, patients with Noonan syndrome may have abdominal swelling and low proteins without complaining and without being aware that this is an abnormality called protein losing enteropathy caused by retrograde flow of chyle into the bowels. Also, patients with the diagnosis primary lymphedema (which implies to be without known cause) may have an anatomic or functional abnormality of the lymph vessels, that is not diagnosed as the causative lymph flow problem. Patients with a cardiac condition called Fontan circulation may have ascites and protein losing enteropathy while others have not. It is unknown what the causative mechanism is.
Currently, there is no protocol for diagnosing lymph flow disorders. In many

cases the diagnosis is based on the symptoms and not on the underlying abnormal lymph anatomy or flow. There are tests for the lymph flow, such as lymph scintigraphy, however this has a very low spatial and temporal resolution. Some institutions use MR T2 images, which images fluid (lymph), but not flow.
Recently the dynamic MR lymphangiography (DMRL) with intranodal contrast injection was introduced in the Radboudumc, based on the scan invented in Philadelphia. With this DMRL scan the flow of lymph in the central lymph vessels is visualized, to diagnose anatomic and flow abnormalities. This dynamic imaging is the gate to improving therapy such as minimal invasive embolization of leakages. However the DMRL has not been validated yet and it has not been studied what the additive value is compared to conservative or non-invasive tests.
With the diagnosis being based on the symptoms and not on the underlying cause, as a consequence the therapy will focus on diminishing symptoms and not healing the pathological cause. For primary lymph edema, the current therapy is bandaging; however the probable cause is found in abnormal retrograde lymph flow and aberrant lymph vessels. For chylothorax, the current therapy is drainage, however the cause being a leak in the thoracic duct is rarely examined nor subject of therapy. It is important to gain more knowledge of the pathophysiology in order to improve therapy.
This study is researching several aspects of lymph, as described in the objective. The aim of this study is to help the patients with lymph flow disorders. Due to the lack of current research, this is accomplished by first aiming for improving the basic knowledge of lymph anatomy, lymph flow and lymph velocity in healthy volunteers. Thereafter, abnormalities could be easier recognized and possibly treated.

Study objective

To improve the knowledge and understanding of the (patho)physiology of lymph disorders
Main objective: the anatomy of the central lymph vessels, the velocity and direction of lymph flow and its influencers and thoracic duct outlet location and patency.

Study design

This is a single center, prospective collection of data of MR lymphangiography and contrast-enhanced ultrasound imaging in our center. The anatomy of the central lymph vessels will be studied. The MR lymphangiography scans will also be reviewed for measurements such as the width of the thoracic duct and the location of inflow into the subclavian vein. The velocity of the lymph flow will be measured on the MR images that were made after intranodal contrast injection. In addition, thoracic duct outlet location and patency will be determined using contrast-enhanced ultrasound imaging of the left and right neck.

Study burden and risks

Participation places subjects at minimal risk. The health benefit of this study for the healthy volunteers is zero, the incentive is the benefit for the subjects. Subjects will undergo placement of a small needle in an inguinal lymph node on both sides , with very little risk of bleeding and/or infection, as with other minimal invasive procedures. The contrast agent used for the DMRL and used for contrast-enhanced ultrasound imaging carries minimal risk of adverse reaction. The dynamic MR lymphangiography will take approximately two hours. In the Radboudumc, around 70 patients undergone the DMRL, all without complications.

During this study, there may be incidental findings that are not relevant for the study, but are for the subject. If this is important for the subjects health, . the primary care physician will be informed by de study coordinator in case of an incidental finding. The subject will also consent to this.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- 18 years and older (no restriction for sex)
- willing and able to have dynamic MR scanning in the Radboudumc
- written informed consent

Exclusion criteria

- unsuitable for MRI (metallic object in the body, severe claustrophobia)
- pregnancy
- kidney problems
- liver cirrhosis
- cardiovascular disease
- medication use

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-04-2023
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Gadolinium-Based Contrast Agent + Sulfur hexafluoride lipid-type A microspheres

Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	05-01-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL76213.091.21