Project Summary

SWISS LIPID RESEARCH AWARD 2017 – SPONSORED BY AMGEN

Retinal vessel analysis in dyslipidemia: The eye, a window to the body's microcirculation

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Background:

Dyslipidemia represents one of the most important risk factors for atherosclerosis. An early phenomenon observed in the process of atherosclerosis is endothelial dysfunction, a state characterized by impaired vasodilatation, vessel wall integrity and blood coagulation.[1] Hypercholesterolemia is an important risk factor for endothelial dysfunction.[2]

While methods quantifying endothelial dysfunction in larger conduit vessels are well established, there is a lack of non-invasive and reproducible ways to measure endothelial function in the microcirculation. Retinal vessel analysis (RVA) is a novel and unique method allowing measurement of the dynamic, endothelial-dependent dilatation of small retinal arterioles and venules in response to flicker light using fundus videography.[3] We recently showed that there is profound retinal microvascular dysfunction in patients with heart failure.[4] Less is known on hypercholesterolemia, an important risk factor for ischemic heart failure and other cardiovascular diseases.

Specific aims:

The goals of this project are to:

1. Study the extent of retinal microvascular dysfunction as measured with flicker-light induced dilatation of arterioles and venules (FID_{art} and FID_{ven} respectively) in patients with hypercholesterolemia compared to healthy controls (HC) and established measures of vascular function (arteriovenous ratio [AVR], pulse wave velocity [PWV], augmentation index [AIX] and flow-mediated dilatation [FMD])
2. Study the association of cholesterol levels with FID_{art} and secondary vascular parameters (FID_{ven}, AVR, PWV, AIX and FMD).
3. Study the effect of lipid-lowering drugs (statins and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) on retinal microvascular dysfunction

Methods:

Study design and protocol

In this prospective, ethics approved study, patients with hypercholesterolemia defined as either preexisting treatment with a lipid-lowering drug (statin or PCSK9 inhibitor) or untreated patients with LDL cholesterol of 4.1 mmol/L or greater as well as HC are recruited for measurement of vascular function at the University Hospital Zurich, Switzerland. Exclusion criteria include any cardiovascular disease, diabetes mellitus, smoking and significant eye diseases. Previously treatment-naïve patients on planned lipid-lowering therapy with statins or PCSK9 inhibitors (n=40) will be assessed before, 3 months after and 1 year after start of therapy.

Retinal vessel analysis

RVA is conducted using an Imedos Dynamic Retinal Vessel Analyzer (Imedos, Jena, Germany). Previously established and validated protocols are used in this study.[3]

Flow-mediated vasodilatation

FMD is measured using established protocols with ultrasound-based measurement of brachial artery diameter before and after blood pressure cuff occlusion.[5]

Arterial stiffness

Arterial stiffness (AIX and PVW) is measured with a SphygmoCor applanation tonometer (AtCor Medical, Itasca, IL, USA) according to established protocols.[6]

Laboratory assessments

Blood samples are taken in the fasted state and analyzed on the same day at the Institute of Clinical Chemistry, University Hospital Zurich with established methods.

Statistical analysis

The primary endpoint of the study is the difference in FID_{art} between patients with hypercholesterolemia and HC. The other vascular measurements (FID_{ven}, AVR, FMD, PWV and AIX) are secondary exploratory outcomes. Sample size is estimated based on data on FID_{art} of HC by Mandecka *et al*.[7] Estimating a difference of FID_{art} of 1% (SD 2.1) with power of 80% and an alpha error of 5%, a group size of 70 patients per group was determined.

Preliminary results:

We recruited 78 HC (mean age 61.8 ± 11.2 years; 45% female) and 67 patients with hypercholesterolemia (mean age 64.4 ± 10.4 years; 45% female). There was a significant difference in primary endpoint with lower FID_{art} in patients with hypercholesterolemia compared to HC (mean FID_{art} 2.1 ± 1.8 vs. 3.1 ± 1.8%, p=0.001). LDL cholesterol was a significant negative predictor of FID_{art} (β=-0.45, p=0.007) in multiple regression analysis adjusted for BMI, systolic BP, lipid-lowering or antihypertensive therapy and HDL cholesterol (F(7,143) ratio=2.2, r^2=0.10, r^2 adj=0.06, p=0.04).

Expected value of proposed project:

There is accumulating evidence that the microcirculation plays an important role in the development of cardiovascular diseases.[8] Preliminary results of our project show that hypercholesterolemia is associated with retinal microvascular dysfunction as evidenced by reduced flicker-induced dilatation of retinal arterioles. This provides important information for ophthalmologists or cardiologists that are interested in using the eye as a window to the microcirculation of the body. In primary prevention, RVA may be useful for stratifying and identifying patients at elevated cardiovascular risk. Due to the dynamic nature of the measurement, flicker-induced dilatation may be a good response marker for lipid-lowering

therapies. This projects further aims to characterize the effect of statin therapy and PCSK9 inhibition on retinal microvascular dysfunction which has not been assessed so far. RVA may provide useful longitudinal information for patients on these therapies as the resolution of endothelial dysfunction may be an early marker of treatment success or failure, allowing further optimization of therapy.

Funding:

The study is funded by grants from the University Hospital Zurich, the Zurich Heart House, the LHW foundation and the Swiss Heart Foundation.

Conflict of Interest Statements:

M.P.N., J.B., F.E.: Nothing to declare.

I.S.: Non-financial support, travel grants und personal fees from Amgen, Servier, Sanofi Aventis, MSD, grants from the Swiss Heart Foundation.

F.R.: Personal fees from Servier, personal fees from Cardiorentis, grants and personal fees from Biotronik.

A.J.F.: Grants from LHW Foundation and Swiss Heart Foundation; personal fees from Novartis, grants and personal fees from Bayer, non-financial support from Orion Pharma, non-financial support from Amgen, personal fees from Bristol Myers Squibb, personal fees from Mepha.

References:

1. Flammer AJ, Anderson T, Celermajer DS, *et al.* The assessment of endothelial function: from research into clinical practice. Circulation 2012;**126**(6):753-67.
2. Landmesser U, Hornig B, Drexler H. Endothelial dysfunction in hypercholesterolemia: mechanisms, pathophysiological importance, and therapeutic interventions. Semin Thromb Hemost 2000;**26**(5):529-37.
3. Heitmar R, Summers RJ. Assessing vascular function using dynamic retinal diameter measurements: a new insight on the endothelium. Thromb Haemost 2012;**107**(6):1019-26.
4. Nägele MP, Barthelmes J, Ludovici V, *et al.* Retinal microvascular dysfunction in heart failure. European Heart Journal 2017. Accepted. In Press.
5. Flammer AJ, Anderson T, Celermajer DS, *et al.* The assessment of endothelial function: from research into clinical practice. Circulation 2012;**126**(6):753-67.
6. Laurent S, Cockcroft J, Van Bortel L, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;**27**(21):2588-605.
7. Mandecka A, Dawczynski J, Blum M, *et al.* Influence of flickering light on the retinal vessels in diabetic patients. Diabetes Care 2007;**30**(12):3048-52.
8. Struijker-Boudier HA, Rosei AE, Bruneval P, *et al.* Evaluation of the microcirculation in hypertension and cardiovascular disease. Eur Heart J 2007;**28**(23):2834-40.