两个面向中国的高端诊断工具

1．介绍

诊断在医学上一向起关键的作用：更精确的诊断可以使治疗更有效。下面展示的两种诊断方法在敏感度以及早期疾病勘查能力上有它们的独特性，经由它们可以直接实现更好的治疗选择，也通常可以总体达到更有效预防疾病的目的。

通过这两种方法，病患资料可以快速和准确地被收集起来，它们也适用于筛查基数大的人群。风险病患群可以借此更频繁的接受检查，他们健康状况的变化也可以很快地被检测出来。

为了改善这两种方法的准确性和特异性，一个扩大的包含有关患者样本的数据库是必要的；为此，我们想要邀请适宜的中国医学研究机构和我们一同来系统的建立起这个数据库。

2．视网膜微血管分析

2.1 微血管分析的科学背景

心脏的脉管和视网膜血管具有几个相同的性质，它们在病变过程中也会经历类似的变化。[1][2][3] 视网膜给成像技术以及对微脉管随时间变化的监测提供了便利的位置。视网膜微血管分析深层次的科学依据是建立在如下观察上：心血管问题和疾病先在微血管被观察到，只有过了一段相对长的时间后才同样出现在大一些的血管中；当一个心血管问题在视网膜微血管被探查到，但还没有出现在大的血管中时，就是一个血管风险增大的预测指标，这时通常还留有足够的时间来开展补救措施从而减轻或者彻底避免疾病的突发。

2.2 微血管分析的历史和发展

微血管分析技术起源于美国和欧洲，之后主要在德国和瑞士被发展。[4] 统计研究开始于 20 年前美国的 Larry Hubbard (Atherosclerosis Risk in Communities (ARIC) Study)，在那里，针对免散瞳眼底照相和对视网膜血管异常评估的流程被研发。这项广泛的研究展示了心脏病发作和血管炎症的风险因素。ARIC 研究和 Rotterdam 研究，是众多针对微血管的研究中的两项。[5] [6] [7] [8] [9] [10]

大约 25 年前，Walthard Vilser 博士在耶拿大学(Friedrich-Schiller-University at Jena) 开始了动态血管分析；Vilser 博士随后开创了他自己的公司，开始生产高精确度的光学设备。J.Flammer 教授使用了 Vilser 博士

的设备来对比眼睛微血管的静脉血压和动脉血压；他组合了视网膜动态血管分析 DVA (Dynamic Vessel Analysis)和视网膜静脉分析，并首次确认了青光眼的脉管成因。[2]

2.3 微血管分析的方法

微血管分析可以分成两大部分：静态微血管分析（图 1），和动态微血管分析（图 2）

图 1：静态微血管分析

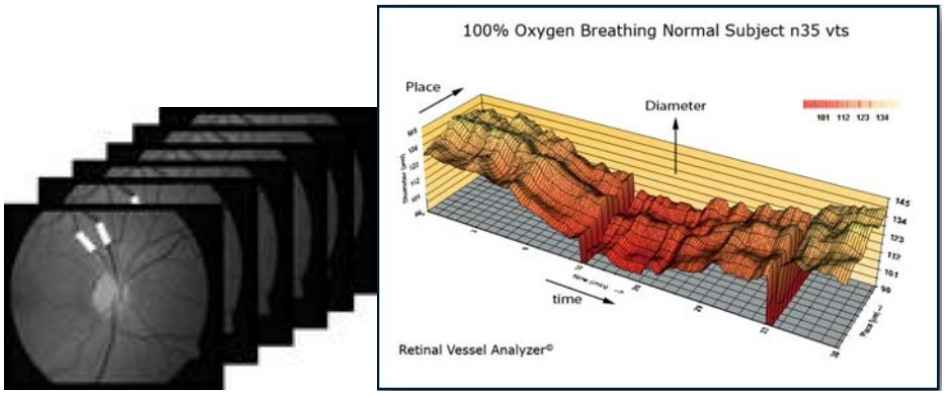
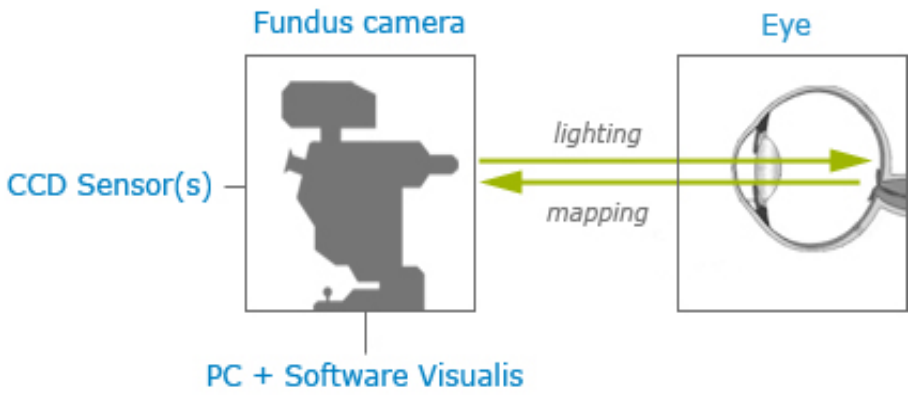


图 2：动态微血管分析

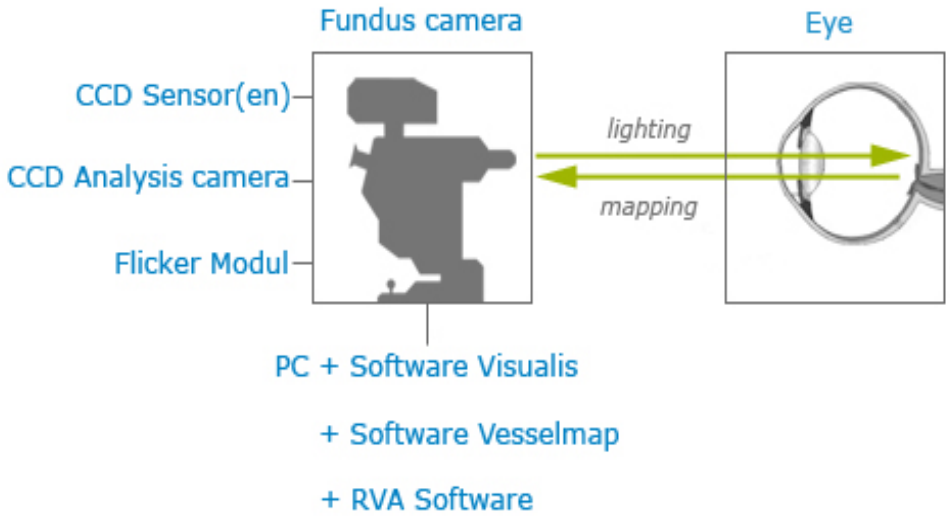
在静态微血管分析中，视网膜微血管被静态分析，即：分析建立在由一台专业相机拍摄的静态图片上，而动态微血管分析分析的是动态的视网膜微血管。在动态微血管分析中，血管直径不仅在一个独立框架中以位置函数被确定，并且继续在一个动态录像中充当时间函数。[11]

2.4 微血管分析的工具

我们提议的工具是 Imedos 视网膜相机：（图 3）



(a)



(b)

图 3：(a) 静态，和 (b) 动态血管分析系统的主要部件

2.5 微血管分析技术的成熟度

静态和动态两种微血管分析现今针对心血管问题的成熟度，已经实现据疾病突发提前多年（5 至 15 年）进行早期诊断。早代设备已经被投入市场，但仍主要应用在眼科上；只有少数几个研究机构开始把该设备应用于普遍心血管分析和疾病预防中。

3. 化学呼吸分析

3.1 化学呼吸分析的科学背景

直接从肺部取样用来诊断可能会有困难。但呼出的呼吸却是一个通往内部代谢的独特窗口，它能以极高的灵敏度和选择性被分析出来。质谱仪可以以极少的样本耗费实现对化学物质检验最高程度的检验精确度。在上世纪 70 年代，鲍林 Linus Pauling 用气相色谱质谱法 GC-MS (gas chromatography-gas chromatography) 针对呼出呼吸的研究引发了人们对呼吸分析的兴趣。[15] 化学呼吸分析的深层理论是建立在如下观察上：每一口被呼出的人类或者动物的呼吸都蕴含着丰富的以化学物质形式存在的信息；这些化学物质通常是极微量的。通过建立在特为此目地研发的并已经被成功验证的质谱仪上的新型设备，微量的特定化学物可以被检验出来。

3.2 化学呼吸分析的历史

用气味来检测人类疾病历史悠久。从希波克拉底到传统中医再到拉瓦锡，直到近 10 年来，它是苏黎世联邦理工学院的重点研究对象。[16]

在那里，分析人类呼吸化学组成迄今为止灵敏度最高的设备被研发。[17][18]19][20][21][22][23]许多学者和研究机构在美国，欧盟和以色列等的支持下努力地发展呼吸诊断技术。2015 年，以色列理工学院的团队宣布，他们研发了一种叫做 NoNose 的呼吸诊断技术，可以由它进行 17 种疾病的检测。[24]

3.3 化学呼吸分析的方法

患者/顾客在常压下呼气到喷雾离子发生器的入管中，在那里，呼吸被离子化，并接着进入到质谱仪的超高真空中。（图 4）

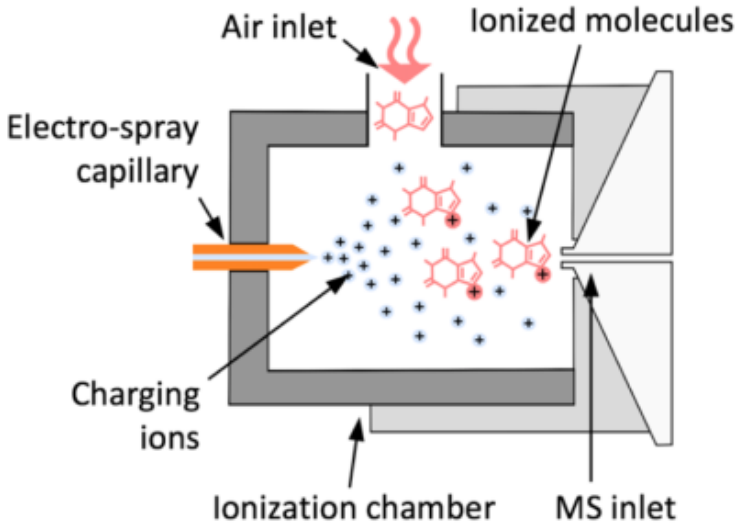


图 4：SESI 离子发生器的构造图

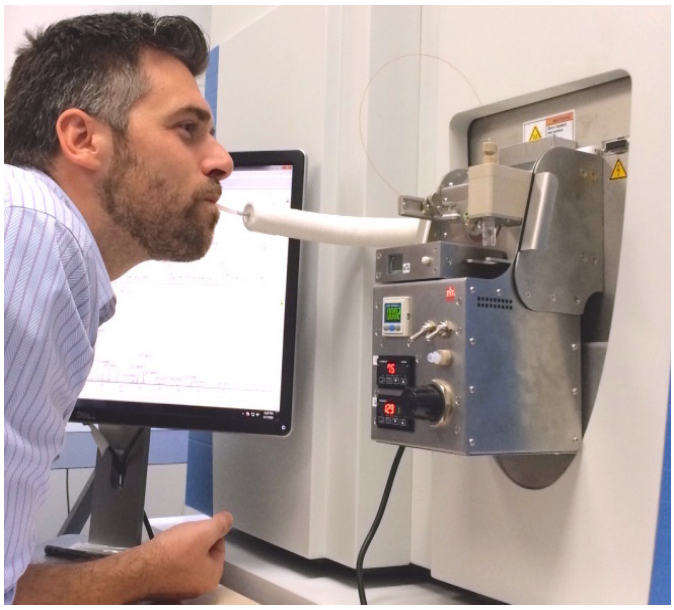


图 5：喷雾离子发生器与一台质谱仪连接进行呼吸分析

3.4 化学呼吸分析的工具

我们提议用来进行化学呼吸分析的工具是 ETH spin-off FIT 的喷雾离子发生器。由 FIT 生产的二次电喷雾电离设备 The Secondary Electro-Spray Ionization (SESI) 使用一种生成带电离子云的电喷雾。这些离子能够电离接触到该电子云的蒸汽。这些电荷转移反应是明确而有效的，而且非常温和（没有高能量参与）。所以，SESI 能够达到：

- 高效的离子化
- 温和的离子化极性物质并不造成裂解
- 瞬时反应

.

3.5 化学呼吸分析的成熟度

化学呼吸分析还处于发展初期阶段。测定人类呼吸中的微量特定分子所需的设备现今是存在的，但仍然价钱昂贵并且复杂。很多问题还有待解决，例如；呼出的重分子黏在设备壁上。新研发的硬件可以克服喷雾离子化的问题并把它们预处理以适应大多数标准的质谱仪；为了能分析每次提交到离子发生器的呼吸中所包含的庞大数据，特定模式的识别软件被开发出来。

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5 附录:

5.1 Various Research Projects / Studies with DVA/RVA

Universität Basel - Institut für Sport- und Sportwissenschaften (ISSW)
Department: sports medicine
Exploratory focus: preventive diagnostics in the field of micro- and

macrovascular vessels, research of the relation between atherosclerotic risc factors and parameters of retinal vessel analysis (static and dynamic) regarding to vessel structure and -function
Contact: PD Dr. A. Schmidt- Trucksäss, Dr.med. Henner Hanssen

Allgemeines Krankenhaus Wien
Department: Clinical Pharmacology
Exploratory focus: Vasoactive substances and retinal microcirculation
Contact: Prof. Schmetterer, PD Dr. Garhöfer

Universityhospital Jena, Department: Internal Medicine III; Endocronology and Metabolic disorders
Exploratory focus: Diabetes and Retina / Prediction and Risk indicator
Contact: Prof. Dr. U. A. Müller

Universität Heidelberg
Department: Internal Medicine-Nephrology, Endocrinology / Diabetology / Rheumatology
Exploratory focus: Obesity - Metabolic Syndrome
Contact: Prof. Dr. med. Hans-Peter Hammes

Universität München
Department: Sports and Preventive Medicine with interdisciplinary co-operation
Exploratory focus: Preventive Medicine; Reference Values of healthy people; Values in patients with metabolic syndrome, coarctation of aorta, hypertension, diabetes, coronary artery disease
Contact: Prof. Halle, PD Dr. Schmidt- Trucksäss, Dr. Pressler

Augenklinik der TU München
Department: Ophthalmology with interdisciplinary co-operation
Exploratory focus: Clinical-experimental examinations to the methodology; Vascular eye diseases
Contact: Prof. Dr. med. Ines Lanzl

Universitätsklinik Dresden
Department: Neurology with interdisciplinary cooperation
Exploratory focus: Morbus Fabry; Autonomous dysfunctions; Diabetes; Therapy impacts
Contact: Dr. Ziemssen

Universitätsspital Basel-Augenklinik
Department: Ophthalmology
Exploratory focus: Glaucoma
Contact: Prof. Flammer
www.glaucomaresearch.ch

Universitäts-Augenklink Dresden
Department: Ophthalmology with interdisciplinary co-operation
Exploratory focus: Retina and cardiovascular diseases; Therapy impacts; Glaucoma
Contact: Prof. Pillunat

University of Montreal
Department: Optometry
Exploratory focus: Physiology of Microcirculation Vascular autoregulation, Neuro-vascular
coupling. Senescence and vascular responsivity.
Contact: Prof. John Vincent Lovasik, Prof. Kergoat

Klinik Heringsdorf
Department: Paediatrics
Exploratory focus: Adiposity and Diabetes infantile
Contact: PD Prof. Schiel

Clinical Investigation Center Paris
Exploratory focus: Arterial Hypertension - Retinal Occlusive Diseases

Contact: Prof. Paques

Universitätsklinikum Greifswald - Klinik und Poliklinik für Augenheilkunde
Exploratory focus: reference ranges, prevention (sports)

5.2 Selected abstracts of related research papers:

5.2.1 Micro Vessel Analysis

Title: The Relation of Retinal Vessel Caliber to the Incidence and Progression of Diabetic Retinopathy XIX: The Wisconsin Epidemiologic Study of Diabetic Retinopathy
Date: 2004
Authors: Ronald Klein, MD, MPH; Barbara E. K. Klein, MD; Scot E. Moss, MA

Abstract:
Objective: To describe the relation of retinal arteriolar and venular caliber to the incidence and progression of diabetic retinopathy in people with type1 diabetes mellitus.

Design: Incidence findings in a population-based study of diabetic retinopathy in Wisconsin. Participants included 996 persons diagnosed as having diabetes mellitus before 30 years of age who took insulin and underwent the baseline examination, 891 in the 4-year follow-up, 765 in the 10-year follow-up, and634 in the 14-year follow-up. Retinal photographs of 7 standard fields were taken at all examinations. Computer-assisted grading was performed from a digitized image of field 1 to determine the average diameter of retinal arterioles and venules and their ratio. Main outcome measures included incidence and progression of retinopathy, incidence of proliferative retinopathy, and macular edema.

Results: While adjusting for other factors, larger arteriolar (relative risk[RR] for the fourth vs first quartile range, 2.04; 95% confidence interval[CI], 1.20-3.47; test of

trend, P = .008) and venular diameters (RR, 2.33; 95% CI, 1.37-3.95; test of trend, P = .005) were associated with greater 4-year progression of retinopathy. Larger venular diameters (RR, 4.28; 95% CI, 1.50-12.19; test of trend, P = .006) but not arteriolar diameters were associated with greater 4-year incidence of proliferative retinopathy. In multivariable analyses, arteriolar and venular calibers were not associated with the 4-yearincidence of retinopathy. While adjusting for other factors, arteriolar and venular calibers were not associated with incidence of macular edema at 4years. There were few associations of arteriolar or venular caliber with the10- or 14-year incidence or the progression of retinopathy.

Conclusions: Larger arteriolar and venular caliber, independent of retinopathy severity level, is related to the progression of retinopathy, and larger venular caliber is associated with the 4-year incidence of proliferative retinopathy. Caliber of retinal vessels is not associated with incident retinopathy. These data suggest a quantitative measure of retinal vascular caliber provides additional information regarding risk for progression of retinopathy.

Published: Klein, R., Klein, B. E., Moss, S. E., Wong, T. Y., Hubbard, L., Cruickshanks, K. J., & Palta, M. (2004). The Relation of Retinal Vessel Caliber to the Incidence and Progressionof Diabetic Retinopathy: XIX: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Archives of ophthalmology, 122(1), 76-83

Title: Retinal Vessel Diameters and Risk of Hypertension
Date: 2006
Authors: M. Kamran Ikram, Jacqueline C.M. Witteman, Johannes R. Vingerling, Monique M.B. Breteler, Albert Hofman and Paulus T.V.M. de Jong

Abstract: Generalized retinal arteriolar narrowing is an important sign of systemic hypertension, and a lower arteriolar: venular diameter ratio predicts the risk of hypertension. We investigated whether this association was based on arteriolar or venular diameters or both. This study was based on the prospective population–based Rotterdam Study (1990–1993) and included 1900 participants (55 years of

age) of whom 739 persons had normal blood pressure (systolic 120 mm Hg and diastolic 80 mm Hg) and 1161 prehypertension (systolic 120 to 139 mm Hg or diastolic 80 to 89 mm Hg). For each participant, retinal arteriolar and venular diameters were measured on digitized images of 1 eye. After a mean follow-up of 6.6 years, 808 persons developed hypertension, defined as either systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mm Hg or use of antihypertensive medication. Adjusted for age, gender, follow-up time, body mass index, smoking, diabetes mellitus, total and high-density lipoprotein cholesterol, C-reactive protein, and intima–media thickness, arteriolar narrowing was associated with an increased risk of hypertension (odds ratio per SD: 1.38; 95% CI, 1.23 to 1.55); for venular narrowing this was less striking (OR: 1.17; 95% CI, 1.04 to 1.32). Each SD decrease in the arteriolar: venular diameter ratio significantly increased the risk of hypertension by 24%. To examine the effect of baseline blood pressure, we stratified persons into those with "normal blood pressure" or "prehypertension." Within these strata, arteriolar narrowing was still related to incident hypertension. These data show that both retinal arteriolar and venular narrowing may precede the development of systemic hypertension. (Hypertension. 2006; 47:189-194.)

Published: Retinal Vessel Diameters and Risk of Hypertension: The Rotterdam Study M. Kamran Ikram, Jacqueline C.M. Witteman, Johannes R. Vingerling, Monique M.B. Breteler, Albert Hofman and Paulus T.V.M. de Jong Hypertension. 2006; 47:189-194; originally published online December 27, 2005; DOI: 10.1161/01.HYP.0000199104.61945.33

Title: Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations

Date: 2007

Authors: Jie Jin Wang, Gerald Liew, Ronald Klein, Elena Rochtchina, Michael D. Knudtson, Barbara E.K. Klein, Tien Yin Wong, George Burlutsky, and Paul Mitchell

Abstract:

Aims: The retinal microvasculature may reflect pre-clinical changes in the cerebral and coronary micro- circulations. We assessed whether smaller retinal arterioles and larger venules predicted coronary heart disease (CHD)- and stroke-mortality.

Methods and results: We pooled data from the Beaver Dam Eye Study (n 1 / 4 4926, aged 43–86) and the Blue Mountains Eye Study (n 1 / 4 3654, aged 49–97). Retinal vessel diameters were measured from digitized retinal photographs. Change point models were used to assess and document the existence of threshold effects. We defined smaller arterioles as diameters within the narrowest quintile and larger venules as diameters within the widest quintile, with other quintiles as the reference. Of 8550 participants, 7494 (88%) with complete data were included, of whom 653 died from CHD and 299 from stroke over 10–12 years follow-up. After multivariable adjustment, each standard deviation (SD) increase in arteriolar diameter, or SD decrease in venular diameter, was not found to be significantly associated with either CHD-mortality or stroke-mortality. However, smaller arterioles [hazard ratio (HR) 1.34, 95% confidence interval (CI) 1.11–1.62] and larger venules (HR 1.24, CI 1.02–1.52), predicted increased risk of CHD-mortality. These associations were mainly evident among persons aged 43–69 (smaller arterioles: HR 1.70, CI 1.27–2.28; larger venules: HR 1.41, CI 1.06–1.89). Smaller arterioles (HR 1.64, CI 1.00–2.67) and larger venules (HR 1.53, CI 0.94–2.47) were also associated with an increased risk of stroke-mortality among persons aged 43–69.

Conclusion: Retinal vessel diameter may predict risk of CHD and stroke deaths in middle-aged persons.

Published: Wang, J. J., Liew, G., Klein, R., Rochtchina, E., Knudtson, M. D., Klein, B. E., ... & Mitchell, P. (2007). Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. European heart journal, 28(16), 1984-1992.

Title: Use of the retinal vessel analyzer in ocular blood flow research

Date: 2009

Authors: Garhofer, G., Bek, T., Boehm, A. G., Gherghel, D., Grunwald, J., Jeppesen, P., ... & Nagel, E.

Abstract: The present article describes a standard instrument for the continuous online determination of retinal vessel diameters, the commercially available retinal vessel analyzer. This report is intended to provide informed guidelines for measuring ocular blood flow with this system. The report describes the principles underlying the method and the instruments currently available, and discusses clinical protocol and the specific parameters measured by the system. Unresolved questions and the possible limitations of the technique are also discussed.

Published: Garhofer, G., Bek, T., Boehm, A. G., Gherghel, D., Grunwald, J., Jeppesen, P., ... & Nagel, E. (2010). Use of the retinal vessel analyzer in ocular blood flow research. Acta ophthalmologica, 88(7), 717-722.

Title: Retinal Vascular Caliber: Systemic, Environmental, and Genetic Associations

Date: 2009

Authors: Cong Sun, MD, MPH, Jie Jin Wang, MMed, PhD, David A. Mackey, MD, Tien Y. Wong, MD, PhD

Abstract: Quantitative studies of retinal vascular caliber using new computer-assisted retinal imaging systems have allowed physicians and researchers to understand the influence of systemic, environmental, and genetic factors on retinal vascular caliber. Retinal vascular caliber changes reflect cumulative response to aging, cardiovascular risk factors, inflammation, nitric oxide–dependent endothelial dysfunction, and other processes. Recent epidemiological studies have shown that changes in retinal arteriolar and venular caliber size may reflect the differential effects of a range of systemic, environmental, and genetic risk factors. Narrower retinal arteriolar caliber and smaller arteriovenous ratio are associated with older age; higher levels of past, current, and future blood pressure and obesity; and predict the incidence of diabetes and coronary heart disease.

Wider retinal venular caliber, in contrast, is associated with younger age; impaired fasting glucose and diabetes; dyslipidemia; obesity; systemic marker of inflammation, endothelial dysfunction, and cigarette smoking; and predicts the risk of stroke and coronary heart disease. New data from family and twin studies indicate a significant genetic contribution to retinal vascular caliber, an area that is under investigation. Elucidating the complete range of systemic, environmental, and genetic factors linked with retinal vascular caliber changes may provide critical insight into the etiology, pathogenesis, and natural history of early vascular disease not only in the eye but elsewhere in the body.

Published: Cong Sun, MD, MPH, Jie Jin Wang, MMed, PhD, David A. Mackey, MD, Tien Y. Wong, MD, PhD. Retinal Vascular Caliber: Systemic, Environmental, and Genetic Associations. Survey of Ophthalmology. Volume 54, Issue 1, January–February 2009, Pages 74–95

Title: Meta-analysis: Retinal Vessel Caliber and Risk for Coronary Heart Disease
Date: 2009
Authors: McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, et al.

Abstract:

Background:

Retinal vessel caliber may be a novel marker of coronary heart disease (CHD) risk. However, the sex-specific effect, magnitude of association, and effect independent of traditional CHD disease risk factors remain unclear.

Purpose:

To determine the association between retinal vessel caliber and risk for CHD.

Data Sources:

Relevant studies in any language identified through MEDLINE (1950 to June 2009) and EMBASE (1950 to June 2009) databases.

Study Selection:

Studies were included if they examined a general population, measured retinal vessel caliber from retinal photographs, and documented CHD risk factors and incident CHD events.

Data Extraction:
6 population-based prospective cohort studies provided data for individual participant meta-analysis.

Data Synthesis:
Proportional hazards models, adjusted for traditional CHD risk factors, were constructed for retinal vessel caliber and incident CHD in women and men. Among 22Â 159 participants who were free of CHD and followed for 5 to 14 years, 2219 (10.0%) incident CHD events occurred. Retinal vessel caliber changes (wider venules and narrower arterioles) were each associated with an increased risk for CHD in women (pooled multivariable-adjusted hazard ratios, 1.16 [95% CI, 1.06 to 1.26] per 20-Î¼m increase in venular caliber and 1.17 [CI, 1.07 to 1.28] per 20-Î¼m decrease in arteriolar caliber) but not in men (1.02 [CI, 0.94 to 1.10] per 20-Î¼m increase in venular caliber and 1.02 [CI, 0.95 to 1.10] per 20-Î¼m decrease in arteriolar caliber). Women without hypertension or diabetes had higher hazard ratios.

Limitation:
Error in the measurement of retinal vessel caliber and Framingham variables was not taken into account.

Conclusion:
Retinal vessel caliber changes were independently associated with an increased risk for CHD events in women.

Published: McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, et al. Meta-analysis: Retinal Vessel Caliber and Risk for Coronary Heart Disease. Ann Intern Med. 2009; 151:404-413. DOI: 10.7326/0003-4819-151-6-200909150-00005

Title: Retinal Vascular Signs: A Window to the Heart?

Date: 2011

Authors: Gerald Liew, Jie Jin Wang

Abstract: There is increasing recognition that coronary microvascular dysfunction also plays an important role in coronary heart disease. Little is known about this aspect of coronary heart disease due to difficulties in studying the coronary microcirculation directly. The retina is a unique site where the microcirculation can be imaged directly, providing an opportunity to study in vivo the structure and pathology of the human circulation and the possibility of detecting changes in microvasculature relating to the development of cardiovascular disease. This review covers the recent progress in research linking retinal vascular signs to coronary heart disease, and finds accumulating evidence that retinal vascular signs may provide a window into the health of the coronary microvasculature. The most widely studied signs, arteriolar narrowing, and more recently, venular dilation, are likely associated with increased risk of coronary heart disease in women, independent of traditional risk factors. Attempts to improve coronary heart disease risk prediction by incorporating retinal vessel caliber size into risk prediction scores complementing traditional algorithms such as the Framingham risk scores have so far been disappointing. Research is ongoing into the predictive utility of other retinal vascular signs. Retinal photography provides long-lasting records that enable monitoring of longitudinal changes in these retinal signs and vascular health.

Published: Gerald Liew and Jie Jin Wang. Retinal Vascular Signs: A Window to the Heart? Published by Elsevier Espan˜a, S.L. Rev Esp Cardiol. 2011;64(6):515–521

Title: Exercise-induced alterations of retinal vessel diameters and cardiovascular risk reduction in obesity.

Date: 2011

Authors: Hanssen H1, Nickel T, Drexel V, Hertel G, Emslander I, Sisic Z, Lorang D, Schuster T, Kotliar KE, Pressler A, Schmidt-Trucksäss A, Weis M, Halle M

Abstract:

Background: The retinal microcirculation is affected early in the process of atherosclerosis and retinal vessel caliber is an emerging cardiovascular risk factor. Obesity is associated with vascular dysfunction. Here, we investigate the effect of regular exercise on retinal vessel diameters in lean and obese runners. We analyze a possible link to alterations of the nitric oxide (NO)-asymmetric dimethylarginine (ADMA) pathway.

Methods: Retinal vessel diameters were assessed by means of a static vessel analyzer (SVA-T) in 15 obese athletes (OA), 14 lean amateur athletes (AA) and 17 lean elite athletes (EA) following a 10-week training program. ADMA serum levels were detected by ELISA and dimethylarginine dimethylaminohydrolase (DDAH) -1/-2 mRNA-expression in peripheral mononuclear cells (PBMC) was analyzed by real time PCR.

Results: At baseline, the mean (±SD) arteriolar to venular diameter ratio (AVR) was impaired in obese (OA: 0.81±0.05) compared to lean subjects (AA: 0.87±0.07; EA: 0.94±0.05). The individual fitness levels correlated with AVR (rho=+0.66; P<0.001) and the training program improved AVR in all groups (P<0.001), normalizing AVR in the obese (OA: 0.86±0.1). A training-induced arteriolar dilatation was found in OA (P=0.01), which was accompanied by a significant decrease of ADMA levels (0.56±0.12-0.46±0.12 µ moll (-1); P<0.028). DDAH-1 mRNA levels in PBMC increased in all groups (P<0.01).

Conclusions: Cardiovascular fitness and body composition affect retinal vessel diameters. Regular exercise reverses the subclinical impairment of the retinal microvasculature in obesity by inducing retinal arteriolar dilatation. The NO/ADMA pathway may play a key role in the training-induced improvement of microvascular function, which has the potential to counteract progression of small vessel disease.

Published: Hanssen H1, Nickel T, Drexel V, Hertel G, Emslander I, Sisic Z, Lorang D, Schuster T, Kotliar KE, Pressler A, Schmidt-Trucksäss A, Weis M, Halle M. 2011 Jun;216(2):433-9. DOI: 10.1016/j.atherosclerosis.2011.02.009. Epub 2011 Feb 17.

Title: Retinal Vessel Caliber and Lifelong Neuropsychological Functioning: Retinal Imaging as an Investigative Tool for Cognitive Epidemiology
Date: 2013
Authors: Idan Shalev, Terrie E. Moffitt, Tien Y. Wong, Madeline H. Meier, Renate M. Houts, Jie Ding, Carol Y. Cheung, M. Kamran Ikram, Avshalom Caspi, and Richie Poulton

Abstracts: Why do more intelligent people live healthier and longer lives? One possibility is that intelligence tests assess health of the brain, but psychological science has lacked technology to evaluate this hypothesis. Digital retinal imaging, a new, noninvasive method to visualize microcirculation in the eye, may reflect vascular conditions in the brain. We studied the association between retinal vessel caliber and neuropsychological functioning in the representative Dunedin birth cohort. Wider venular caliber was associated with poorer neuropsychological functioning at midlife, independently of potentially confounding factors. This association was not limited to any specific test domain and extended to informants' reports of cohort members' cognitive difficulties in everyday life. Moreover, wider venular caliber was associated with lower childhood IQ tested 25 years earlier. The findings indicate that retinal venular caliber may be an indicator of neuropsychological health years before the onset of dementing diseases and suggest that digital retinal imaging may be a useful investigative tool for psychological science.

Published: Psychological Science, 2013; 24(7):1198–1207. DOI:10.1177/0956797612470959
Title: Blood flow in glaucoma
Date: 2005

Author: Matthias C Grieshaber, Josef Flammer

Abstract:

Purpose of review: Glaucoma, one of the leading causes of blindness in the world, is characterized by progressive visual field loss and distinctive excavation of the optic nerve head. Although elevated intraocular pressure is the major risk factor, there is increasing evidence that the pathogenesis of glaucoma is also linked to altered ocular blood flow. This review summarizes the recent publications relevant to blood flow in glaucoma.

Recent findings: Several studies indicate that a perfusion instability, rather than a steady reduction of ocular blood flow, might contribute to glaucomatous optic neuropathy. The main cause of the instability is a disturbed autoregulation in the context of a general vascular dysregulation. The underlying mechanism of such a vascular dysregulation is not known. A dysfunction of both the autonomic nervous system and vascular endothelial cells is discussed.

Summary: The mechanical and vascular theories are not mutually exclusive; on the contrary, a vascular dysregulation increases the susceptibility to intraocular pressure. Therapeutically, therefore, both an intraocular pressure reduction and an improvement of the ocular blood flow might be considered.

Published: Grieshaber, Matthias C; Flammer, Josef. Current Opinion in Ophthalmology: 16(2); DOI: 10.1097/01.icu.0000156134.38495.0b. Glaucoma

Title: What Is the Link Between Vascular Dysregulation and Glaucoma?
Date: 2007
Author: Matthias C. Grieshaber, MD, FEBO, Maneli Mozaffarieh, MD, Josef Flammer, MD

Abstract: The need of blood flow to different organs varies rapidly over time which is why there is sophisticated local regulation of blood flow. The term dysregulation simply means that blood flow is not properly adapted to this need. Dysregulative mechanisms can lead to an over- or under perfusion. A steady over perfusion may be less critical for long-term damage. A constant under perfusion, however, can lead to some tissue atrophy or in extreme situations to infarction. Unstable perfusion (under perfusion followed by reperfusion) leads to oxidative stress. There are a number of causes that lead to local or systemic vascular dysregulation. Systemic dysregulation can be primary or secondary of nature. A secondary dysregulation is due to other autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, systemic lupus erythematodes, multiple sclerosis, colitis ulcerosa, or Crohns disease. Patients with a secondary vascular dysregulation normally have a high level of circulating endothelin-1 (ET-1). This increased level of ET-1 leads to a reduction of blood flow both in the choroid and the optic nerve head but has little influence on autoregulation. In contrast, primary vascular dysregulation has little influence on baseline ocular blood flow but interferes with autoregulation. This, in turn, leads to unstable oxygen supply, which seems to be a relevant component in the pathogenesis of glaucomatous optic neuropathy.

Published: Matthias C. Grieshaber, MD, FEBO, Maneli Mozaffarieh, MD, Josef Flammer, MD, (2007), Suvery of Ophthalmology: 52(6);144-154. DOI: 10.1016/j.survophthal.2007.08.010

Title: The primary vascular dysregulation syndrome: implications for eye diseases
Date: 2013
Author: Flammer, J., Konieczka, K., & Flammer, A. J.

Abstract: Vascular dysregulation refers to the regulation of blood flow that is not adapted to the needs of the respective tissue. We distinguish primary vascular dysregulation (PVD, formerly called vasospastic syndrome) and secondary vascular dysregulation (SVD). Subjects with PVD tend to have cold extremities, low

blood pressure, reduced feeling of thirst, altered drug sensitivity, increased pain sensitivity, prolonged sleep onset time, altered gene expression in the lymphocytes, signs of oxidative stress, slightly increased endothelin-1 plasma level, low body mass index and often diffuse and fluctuating visual field defects. Coldness, emotional or mechanical stress and starving can provoke symptoms. Virtually all organs, particularly the eye, can be involved. In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. Subjects with PVD have increased risk for normal-tension glaucoma, optic nerve compartment syndrome, central serous choroidopathy, Susac syndrome, retinal artery and vein occlusions and anterior ischaemic neuropathy without atherosclerosis. Further characteristics are their weaker blood- brain and blood-retinal barriers and the higher prevalence of optic disc haemorrhages and activated astrocytes. Subjects with PVD tend to suffer more often from tinnitus, muscle cramps, migraine with aura and silent myocardial ischaemic and are at greater risk for altitude sickness. While the main cause of vascular dysregulation is vascular endotheliopathy, dysfunction of the autonomic nervous system is also involved. In contrast, SVD occurs in the context of other diseases such as multiple sclerosis, retrobulbar neuritis, rheumatoid arthritis, fibromyalgia and giant cell arteritis. Taking into consideration the high prevalence of PVD in the population and potentially linked pathologies, in the current article, the authors provide recommendations on how to effectively promote the field in order to create innovative diagnostic tools to predict the pathology and develop more efficient treatment approaches tailored to the person.

Published: Flammer, J., Konieczka, K., & Flammer, A. J. (2013), The primary vascular dysregulation syndrome: implications for eye diseases. Epma j, 4(1), 14

Title: The eye and the heart
Date:2013
Author: Flammer, J; Konieczka, K; Bruno, R M; Virdis, A; Flammer, A J; Taddei, S

Abstract: The vasculature of the eye and the heart share several common characteristics. The easily accessible vessels of the eye are therefore-to some extent-a window to the heart. There is interplay between cardiovascular functions and risk factors and the occurrence and progression of many eye diseases. In particular, arteriovenous nipping, narrowing of retinal arteries, and the dilatation of retinal veins are important signs of increased cardiovascular risk. The pressure in the dilated veins is often markedly increased due to a dysregulation of venous out ow from the eye. Besides such morphological criteria, functional alterations might be even more relevant and may play an important role in future diagnosetics. Via neurovascular coupling, flickering light dilates capillaries and small arterioles, thus inducing endothelium-dependent, ow-mediated dilation of larger retinal vessels. Risk factors for arteriosclerosis, such as dyslipidaemia, diabetes, or systemic hypertension, are also risk factors for eye diseases such as retinal arterial or retinal vein occlusions, cataracts, age-related macular degeneration, and increases in intraocular pressure (IOP). Functional alterations of blood ow are particularly relevant to the eye. The primary vascular dysregulation syndrome (PVD), which often includes systemic hypotension, is associated with disturbed autoregulation of ocular blood ow (OBF). Fluctuation of IOP on a high level or blood pressure on a low-level lead to instable OBF and oxygen supply and therefore to oxidative stress, which is particularly involved in the pathogenesis of glaucomatous neuropathy. Vascular dysregulation also leads to a barrier dysfunction and thereby to small retinal haemorrhages.

Published: Flammer, J., Konieczka, K., Bruno, R. M., Virdis, A., Flammer, A. J., & Taddei, S. (2013), The eye and the heart. European heart journal, 34(17), 1270-1278

Title: Diagnosis and Classification of Diseases from 1404 Subjects via Pattern Analysis of Exhaled Molecules

Date:2015

Author: Morad K. Nakhleh,† Haitham Amal, Raneen Jeries,† Yoav Y. Broza

Abstract: We report on an artificially intelligent nanoarray based on molecularly modified gold nanoparticles and a random network of single-walled carbon nanotubes for noninvasive diagnosis and classification of a number of diseases from exhaled breath. The performance of this artificially intelligent nanoarray was clinically assessed on breath samples collected from 1404 subjects having one of 17 different disease conditions included in the study or having no evidence of any disease (healthy controls). Blind experiments showed that 86% accuracy could be achieved with the artificially intelligent nanoarray, allowing both detection and discrimination between the different disease conditions examined. Analysis of the artificially intelligent nanoarray also showed that each disease has its own unique breathprint, and that the presence of one disease would not screen out others. Cluster analysis showed a reasonable classification power of diseases from the same categories. The effect of confounding clinical and environmental factors on the performance of the nanoarray did not significantly alter the obtained results. The diagnosis and classification power of the nanoarray was also validated by an independent analytical technique, i.e., gas chromatography linked with mass spectrometry. This analysis found that 13 exhaled chemical species, called volatile organic compounds, are associated with certain diseases, and the composition of this assembly of volatile organic compounds differs from one disease to another. Overall, these findings could contribute to one of the most important criteria for successful health intervention in the modern era, viz. easy-to-use, inexpensive (affordable), and miniaturized tools that could also be used for personalized screening, diagnosis, and follow-up of a number of diseases, which can clearly be extended by further development.

Published: Nakhleh, M. K., Amal, H., Jeries, R., Broza, Y. Y., Aboud, M., Gharra, A., ... & Glass-Marmor, L. (2016). Diagnosis and Classification of 17 Diseases from 1404 Subjects via Pattern Analysis of Exhaled Molecules. ACS nano.

5.2.2 Chemical Breath Analysis

Title: Human breath analysis may support the existence of individual metabolic phenotypes
Date: 2013
Author: Martinez-Lozano Sinues, Pablo; Kohler, Malcolm; Zenobi, Renato

Abstract: The metabolic phenotype varies widely due to external factors such as diet and gut microbiome composition, among others. Despite these temporal fluctuations, urine metabolite profiling studies have suggested that there are highly individual phenotypes that persist over extended periods of time. This hypothesis was tested by analyzing the exhaled breath of a group of subjects during nine days by mass spectrometry. Consistent with previous metabolomics studies based on urine, we conclude that individual signatures of breath composition exist. The confirmation of the existence of stable and specific breath prints may contribute to strengthen the inclusion of breath as a bio fluid of choice in metabolomics studies. In addition, the fact that the method is rapid and totally non-invasive, yet individualized profiles can be tracked, makes it an appealing approach.

Published: Martinez-Lozano Sinues P, Kohler M, Zenobi R., Human breath analysis may support the existence of individual metabolic phenotypes. (2013), Plos One, 8(4), DOI: 10.1371/journal.pone.0059909;

Title: Circadian variation of the human metabolome captured by real-time breath analysis
Date: 2014
Author: highlight remove highlight from please wait search word highlight Martinez-Lozano Sinues, Pablo; Tarokh, Leila; Li, Xue; Kohler, Malcolm; Brown, Steven A; Zenobi, Renato; Dallmann, Robert

Abstract: Circadian clocks play a significant role in the correct timing of physiological metabolism, and clock disruption might lead to pathological changes of metabolism. One interesting method to assess the current state of metabolism is metabolomics. Metabolomics tries to capture the entirety of small molecules, i.e. the building blocks of metabolism, in a given matrix, such as blood, saliva or urine. Using mass spectrometric approaches, we and others have shown that a significant portion of the human metabolome in saliva and blood exhibits circadian modulation; independent of food intake or sleep/wake rhythms. Recent advances in mass spectrometry techniques have introduced completely non-invasive breath printing; a method to instantaneously assess small metabolites in human breath. In this proof-of-principle study, we extend these findings about the impact of circadian clocks on metabolomics to exhaled breath. As previously established, our method allows for real-time analysis of a rich matrix during frequent non-invasive sampling. We sampled the breath of three healthy, non-smoking human volunteers in hourly intervals for 24 hours during total sleep deprivation, and found 111 features in the breath of all individuals, 36-49% of which showed significant circadian variation in at least one individual. Our data suggest that real-time mass spectrometric "breath printing" has high potential to become a useful tool to understand circadian metabolism, and develop new biomarkers to easily and in real-time assess circadian clock phase and function in experimental and clinical settings.

Published: Martinez-Lozano Sinues P, Tarokh L, Li X, Kohler M, Brown SA, Zenobi R, Dallmann R, Circadian variation of the human metabolome captured by real-time breath analysis. (2014), PLoS One,9(12):e114422.; DOI: 10.1371/journal.pone.0114422;

Title: Breath analysis in real time by mass spectrometry in chronic obstructive pulmonary disease

Date: 2014

Author: Martinez-Lozano Sinues, Pablo; Meier, Lukas; Berchtold, Christian; Ivanov, Mark; Sievi, Noriane; Camen, Giovanni; Kohler, Malcolm; Zenobi, Renato

Abstract: It has been suggested that exhaled breath contains relevant information on health status. OBJECTIVES: We hypothesized that a novel mass spectrometry (MS) technique to analyze breath in real time could be useful to differentiate breath prints from chronic obstructive pulmonary disease (COPD) patients and controls (smokers and nonsmokers). METHODS: We studied 61 participants including 25 COPD patients [Global Initiative for Obstructive Lung Disease (GOLD) stages I-IV], 25 nonsmoking controls and 11 smoking controls. We analyzed their breath by MS in real time. Raw mass spectra were then processed and statistically analyzed. RESULTS: A panel of discriminating mass-spectral features was identified for COPD (all stages; n = 25) versus healthy nonsmokers (n = 25), COPD (all stages; n = 25) versus healthy smokers (n = 11) and mild COPD (GOLD stages I/II; n = 13) versus severe COPD (GOLD stages III/IV; n = 12). A blind classification (i.e. leave-one-out cross validation) resulted in 96% sensitivity and 72.7% specificity (COPD vs. smoking controls), 88% sensitivity and 92% specificity (COPD vs. nonsmoking controls) and 92.3% sensitivity and 83.3% specificity (GOLD I/II vs. GOLD III/IV). Acetone and indole were identified as two of the discriminating exhaled molecules. CONCLUSIONS: We conclude that real-time MS may be a useful technique to analyze and characterize the metabolome of exhaled breath. The acquisition of breath prints in a rapid manner may be valuable to support COPD diagnosis and to gain insight into the disease.

Published: Martinez-Lozano Sinues P, Meier L, Berchtold C, Ivanov M, Sievi N, Camen G, Kohler M, Zenobi R, Breath analysis in real time by mass spectrometry in chronic obstructive pulmonary disease. (2014), Respiration, 87(4):301-310; DOI: 10.1159/000357785; 10.1159/000357785

Title: Identification of 2-Alkenals, 4-Hydroxy-2-alkenals, and 4-Hydroxy-2,6-alkadienals in Exhaled Breath Condensate by UHPLC-HRMS and in Breath by Real-Time HRMS

Date: 03,03,2015

Author: Diego García-Gómez, Pablo Martínez-Lozano Sinues, César Barrios-Collado, Guillermo Vidal-de-Miguel, Martin Gaugg, and Renato Zenobi

Abstract: In recent years, breath analysis in real time has become a noninvasive alternative for the diagnosis of diseases and for molecular fingerprinting of exhaled breath. However, the techniques used lack the capabilities for proper identification of the compounds found in the exhalome. Here, we report the use of UHPLC-HRMS as a tool for the identification of several aldehydes (2-alkenals, 4-hydroxy-2-alkenals, and 4-hydroxy-2,6-alkadienals), biomarkers of lipid peroxidation, in exhaled breath condensate of three healthy subjects (N = 3). Some of the aldehydes studied have never been identified before. Their robust identification is based on retention times, on the generation of fragmentation trees from tandem mass spectra, and on the comparison of these parameters with standards. We also show that the identified compounds can be analyzed and confirmed by MS/MS in breath in real time and, therefore, they could be used as biomarkers for the rapid and noninvasive diagnosis of related diseases.

Published: García-Gómez D, Martínez-Lozano Sinues P, Barrios-Collado C, Vidal-de-Miguel G, Gaugg M, Zenobi R, Identification of 2-alkenals, 4-hydroxy-2-alkenals, and 4-hydroxy-2,6-alkadienals in exhaled breath condensate by UHPLC-HRMS and in breath by real-time HRMS, (2015), Analysis Chemistry, 87 (5):3087–3093; DOI: 10.1021/ac504796p

Title: Drug pharmacokinetics determined by real-time analysis of mouse breath
Date: 2015
Author: Li, Xue ; Martinez-Lozano Sinues, Pablo ; Dallmann, Robert ; Bregy, Lukas ; Hollmén, Maija ; Proulx, Steven ; Brown, Steven A ; Detmar, Michael ; Kohler, Malcolm ; Zenobi, Renato

Abstract: Noninvasive, real-time pharmacokinetic (PK) monitoring of ketamine, propofol, and valproic acid, and their metabolites was achieved in mice, using secondary electrospray ionization and high-resolution mass spectrometry. The PK

profile of a drug influences its efficacy and toxicity because it determines exposure time and levels. The antidepressant and anaesthetic ketamine (Ket) and four Ket metabolites were studied in detail and their PK was simultaneously determined following application of different sub-anaesthetic doses of Ket. Bioavailability after oral administration vs. intraperitoneal injection was also investigated. In contrast to conventional studies that require many animals to be sacrificed even for low-resolution PK curves, this novel approach yields real-time PK curves with a hitherto unmatched time resolution (10 s), and none of the animals has to be sacrificed. This thus represents a major step forward not only in animal welfare, but also major cost and time savings.

Published: Li X, Martinez-Lozano Sinues P, Dallmann R, Bregy L, Hollmén M, Proulx S, Brown SA, Detmar M, Kohler M, Zenobi R, Drug Pharmacokinetics Determined by Real-Time Analysis of Mouse Breath (2015), Angewandte Chemie Internationale Edition, 54(27):7815-7818; DOI: 10.1002/anie.201503312; 10.1002/anie.201503312

Title: Real-Time High-Resolution Tandem Mass Spectrometry Identifies Furan Derivatives in Exhaled Breath
Date: 07,07,2015
Author: Diego García-Gómez, Lukas Bregy, César Barrios-Collado, Guillermo Vidal-de-Miguel, and Renato Zenobi

Abstract: The identification of chemical compounds in exhaled human breath is promising in the search for new biomarkers of diseases. However, the analytical techniques used nowadays are not capable of achieving a robust identification, especially in real-time analysis. In this work, we show that real-time high-resolution tandem mass spectrometry (HRMS/MS) is suitable for the identification of biomarkers in exhaled breath. Using this approach, we identified a number of furan derivatives, compounds found in the exhalome whose nature and origin are not yet clearly understood. It is also shown that the combination of HRMS/MS

with UHPLC allowed not only the identification of the furan derivatives but also the proper separation of their isomeric forms.

Published: García-Gómez D, Bregy L, Barrios-Collado C, Vidal-de-Miguel G, Zenobi R, Real-Time High-Resolution Tandem Mass Spectrometry Identifies Furan Derivatives in Exhaled Breath, (2015), Analytical Chemistry, 87(13):6919-6924; DOI: 10.1021/acs.analchem.5b01509

Title: Expanding metabolite coverage of real-time breath analysis by coupling a universal secondary electrospray ionization source and high resolution mass spectrometry - a pilot study on tobacco smokers
Date: 2016
Author: Gaugg, Martin Thomas; Gomez, Diego Garcia ; Barrios-Collado, Cesar ; Vidal-de-Miguel, Guillermo ; Kohler, Malcolm ; Zenobi, Renato ; Martinez-Lozano Sinues, Pablo

Abstract: Online breath analysis is an attractive approach to track exhaled compounds without sample preparation. Current commercially available real-time breath analysis platforms require the purchase of a full mass spectrometer. Here we present an ion source compatible with virtually any preexisting atmospheric pressure ionization mass spectrometer that allows real-time analysis of breath. We illustrate the capabilities of such technological development by upgrading an orbitrap mass spectrometer. As a result, we detected compounds in exhaled breath between 70 and 900 Da, with a mass accuracy of typically<1 ppm; resolutions between m/Δm 22,000 and 70,000 and fragmentation capabilities. The setup was tested in a pilot study, comparing the breath of smokers (n=9) and non-smokers (n=10). Exogenous compounds associated to smoking, as well as endogenous metabolites suggesting increased oxidative stress in smokers, were detected and in some cases identified unambiguously. Most of these compounds correlated significantly with smoking frequency and allowed accurate discrimination of smokers and non-smokers.

Published: Gaugg MT, Gomez DG, Barrios-Collado C, Vidal-de-Miguel G, Kohler M, Zenobi R, Martinez-Lozano Sinues P, Expanding metabolite coverage of real-time breath analysis by coupling a universal secondary electrospray ionization source and high resolution mass spectrometry--a pilot study on tobacco smokers, (2016), Journal of breath research, 10(1):016010; DOI: 10.1088/1752-7155/10/1/016010