doi:10.3969/j.issn.1009-6469.2019.03.053 ◇专论◇

呼出气挥发性有机化合物在临床转化医学中的应用

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摘要:人体呼出气中含有数千种挥发性有机化合物,反映着体内的代谢状况。近年来呼出气分析技术由于它的方便,安全,无创和无痛等优点,使它在临床诊断和监测领域中备受关注。多项研究表明,特异性的挥发性有机化合物与某些疾病存在相关性,可作为疾病诊断的生物标志物。该文总结了与癌症(如肺癌、乳腺癌),代谢性疾病(如糖尿病),氧化应激(如慢性阻塞性肺疾病和哮喘)以及神经系统性疾病(如肌萎缩侧索硬化症、帕金森病)相关的一些呼出气中重要的生物标志物以及产生的病理生理机制。同时简述了呼出气分析技术在临床应用中面临的主要问题。

关键词:呼出气; 生物标志物; 挥发性有机化合物

Application of exhaled volatile organic compounds in clinical transformation medicine

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Abstract: The human exhaled breath contains thousands of volatile organic compounds (VOCs) that reflect the metabolism of human body. In recent years breath analysis,as one of the convnient,safe,noninvasive and painlessness technique,attracts more attention when applying to clinical diagnosis and monitoring of diseases. Severial studies have show that specific volatile organic compounds are associated with certain diseases and can be used as biomakers. This article summarizes some important breath biomakers and their pathophysiological mechanisms associated with cancer(such as lung cancer,breast cancer),metabolic diseases(such as diabetes) oxidative stress (such as chronic obstructive pulmonary disease and asthma) and neurological diseases(such as amyotrophic lateral sclerosis,Parkinson's disease). The main problems in the clinical application of exhaled air analysis are also discussed.

Key words:exhaled breath; biomarkers; volatile organic compounds

呼出气的检测可以追溯到医学发展的早期,在古代,希腊医生就知道呼吸气味与某些疾病有关,可以反映人体的生理病理过程[1]。比如糖尿病病人呼出气中带有甜味,肝脏疾病病人呼出气中的鱼腥味和肾衰竭病人呼出气中尿味。显然,呼出气中的一些物质可以诊断某些疾病或监测体内的代谢过程。

现代呼出气的研究开始于20世纪70年代,Linus Pauling 在人体的呼出气中发现200多种不同的挥发性有机化合物(volatile organic compound,VOCs),证实了人体呼出气成分的复杂性[2]。2017年ACS Nano杂志发表的一篇文章报导使用纳米检测技术对人体呼出气分析,在数分钟内可以诊断包括肺癌等17种疾病,引起了广泛的关注[3]。与血液和尿液分析相比,呼出气分析被认为是既方便又安全的方式,而与传统诊断技术相比,呼出气分析具有无创、操作简单、依从性好以及能够实时监测等优点。目前,基于呼出气分析技术常见的临床应用包括:检查酒后驾驶时测定乙醇和乙醛(乙醇的代谢产物),检测幽门螺杆菌时^{13}C或^{14}C的尿素呼气试验以及识别哮喘时呼出气中NO的检测[4]。在近十几年中,呼出气分析技术对疾病诊断和生物代谢途径分析方面进行了广泛的探索研究,使得一些新的标志物为疾病的诊断和鉴别诊断提供了可能。现对临床应用中呼出气中的重要挥发性标志物进行总结。

1 癌症与呼出气挥发性有机化合物

1.1 肺癌与呼出气挥发性标志物 据世界卫生组织(WHO)称肺癌是导致死亡的主要原因,全世界每年约有159万人死于肺癌[5-6]。肺癌在临床上常用的诊断方法包括血液检查,胸部X线检查,计算机断层扫描(CT),磁共振成像(MRI)和正电子发射断层扫描(PET)等。这些技术只能提供一些有限的信息,如CT扫描技术很难诊断肿瘤的良恶性以及临

床分期,因此多数情况下需要进行活组织检查,而这种检查方法创伤大,费用高,并且有潜在的出血风险甚至由于出血而导致死亡[7]。

近年来呼出气 VOCs 分析技术对癌症进行了广泛的研究,其中以肺癌的研究数量最多。VOCs 分为外源性和内源性,外源性 VOCs 可以从外部环境中通过吸入或吞食进入体内,然后从呼出气排出,内源性 VOCs 主要是体内代谢过程中的产物。癌症的病人在病理情况下代谢发生变化导致 VOCs 的成分和浓度也发生相应的改变,参与这一变化的主要机制包括:氧化应激的增强,细胞色素 P450 的诱导,碳水化合物代谢(如糖酵解和糖异生途径)和脂质代谢的改变[8]。肺癌病人体内产生的特异性 VOCs 释放到血液中,根据血/气分配系数(λb/a)在肺泡或气道中进行气体交换而排出体外。理论和实验研究表明血液中低溶解度的物质,主要是非极性的 VOCs($\lambda b/a < 10$)几乎完全在肺泡中进行交换,高血溶性的物质主要是极性的 VOCs($\lambda b/a > 100$)往往在气道中进行交换,$100 > \lambda b/a > 10$ 的 VOCs 在肺泡和气道中都有明显的交换[7-8]。表 1 是对近 20 年(按时间顺序)与肺癌有关的一些重要的潜在生物标志物的汇总[9-25]。

1.2 乳腺癌与呼出气挥发性标志物 乳腺癌是最常见的女性恶性疾病之一,也是造成女性死亡的最主要原因。据估计,在美国有超过 350 万名妇女有乳腺癌病史。乳腺癌相比其他癌症更趋向年轻化,平均年龄为 61 岁[26]。它是一种进展性疾病,癌症的早期发现,早期治疗可以有效的降低死亡率。目前乳腺癌最常见的筛查方法有乳腺钼靶 X 线检查,超声检查。钼靶 X 线对乳腺癌的敏感性为 71% ~ 96%,对致密乳腺组织的敏感性更低,乳腺超声检查不能很好的检测到微钙化物质[27]。

近年来已有多篇文献证实乳腺癌病人呼出气中存在特异性的 VOCs(表 2)[27,29-32] 并且对其产生的机制进行了分析。大部分实验结果支持这些化合物来源于氧化应激。癌细胞在恶性生长过程中发生基因突变和蛋白质的表达异常,产生大量的活性氧(ROS)导致细胞膜中的多不饱和脂肪酸被过

表 1 肺癌病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Phillips	2003	Butane 3-methyl tridecane 7-methyl tridecane 5-methyl decane 4-methyl octane 3-methyl hexane heptane 2-methyl hexane pentane
Poli	2005	Decane ethyl benzene isoprene pentamethyl heptane Trimethyl benzene toluene benzene styrene octane heptane
Wehinger	2007	Isopropanol formaldehyde
Chen	2007	Styrene decane isoprene benzene undecane 1-hexene hexanal propyl benzene 1,2,4-trimethyl benzene heptanal methly cyclopentane
Bajtarevic	2009	Isoprene acetone methanol 2-Butanone benzaldehyde 2,3-butanedione 1-propanol
Ligor	2009	1-Propanol 2-butanone 3-butyn-2-ol benzaldehyde n-pentane 2-methyl pentane 3-methyl pentane n-hexane
Kischkel	2010	Dimethyl sulfide
Poli	2010	Nonanal hexanal octanal heptanal butanal pentanal propanal
Song	2010	3-Hydroxy-2-butanone 1-butanol
Fuchs	2010	Pentanal hexanal octanal nonanal
Rudnicka	2011	Isopropyl alcohol styrene carbon disulfide ethylbenzene 2-propenal propane
Ulanowska	2011	Ethanol acetone butane dimethyl sulfide isoprene propanal 1-propanol 2-pentanone furan o-xylene ethylbenzene pentanal hexanal nonane
Buszewski	2012	Butanal 2-butanone ethyl acetate ethylbenzene 2-pentatone 1-propanol 2-propanol
Fu	2014	2-Butanone 2-hydroxyacetaldehyde 3-hydroxy-2-butanone 4-hydroxyhexanal
Handa	2014	n-Dodecane 3-methyl1-1 = butanol 3-methyl-1-butanol 2-methylbutylacetat or 2-hexanol heptanal n-nonal or cyclohexanon isopropylamin ethylbenene hexanal cyclohexanon
Ligorn	2015	Butane 2-methyl-butane 4-methyl octane propene propane 2-pentanone propanal 2,4-dimethylheptanes
Sakumura	2017	Methanol CH3CN isoprene 1-propanol CHN

度氧化,乙烷和戊烷就是由脂肪酸发生过氧化生成[29]。此外 Phillips 认为乳腺癌特异性 VOCs 与雌激素代谢机制的变化和细胞色素 P450 酶活性增加有关,雌激素可以刺激正常的和肿瘤乳腺上皮细胞的增值[28],雌激素的代谢产物起着致癌的作用,其代谢机制的改变可以产生一些特异性的挥发性化合物[27]。此外芳香酶在乳腺癌中高表达,芳香酶是一种雌激素的合成酶,是细胞色素 P450 酶复合体的一部分。其它的 P450 酶在乳腺癌机体内也被激活如 CYR1A1,CYP1B1 和 CYP3A4,P450 酶可以诱导多种生物反应,包括促进烷烃,烯烃和芳香化合物的生物转化[27]。

2 代谢性疾病与呼出气挥发性有机化合物

糖尿病是对人类健康造成重大威胁的主要疾病之一,已成为全球性的流行病。据 WHO 称全球约有 3.5 亿人患有糖尿病,预计到 2030 年将成为第七大死亡原因[33]。糖尿病是一种多变复杂的疾病,几乎影响人体的每一个器官。目前诊断和监测糖尿病的主要方法是检查血糖值,这种方法由于有创常常给病人带来不便。

呼出气 VOCs 分析技术的发展为糖尿病的日常监测和早期诊断提供了可能。已经有大量的研究对糖尿病病人呼出气中的 VOCs 进行分析,呼出气中的丙酮是糖尿病的重要生物标志物,与酮症酸中毒相关[34-35]。血中丙酮水平的升高是糖尿病病人呼出气中“烂苹果”味的主要原因[34]。研究还发现血糖水平和糖尿病病人呼出气中丙酮浓度之间存在很高的相关性[34]。健康者呼出气的丙酮浓度在 0.044 ppm ~ 2.774 ppm 的范围内,1 型糖尿病病人 2.2 ppm ~ 21 ppm 之间,2 型糖尿病在 1.76 ppm ~ 9.4 ppm 之间[33]。因此呼出气丙酮可作为糖尿病的潜在的生物标志物,然而单独的丙酮测定不能很好的诊断糖尿病,因为该浓度受胰岛素抵抗的程度,昼夜波动,脂肪分解活性,饮食成分,性别和禁食状态的影响[35-36]。下表列出了糖尿病病人呼出气中一些重要的生物标志物(表 3)[35,37-38]。

3 氧化应激与呼出气挥发性有机化合物

3.1 慢性阻塞性肺病与呼出气挥发性标志物 据 WHO 称,慢性阻塞性肺病(COPD)是导致死亡的第五大原因,预计到 2030 年将上升至第 3 名[39]。肺功能检查是 COPD 的主要检测方法,但是需要进行反复的呼气,不利于呼吸困难病人的检查。而且它是对肺功能进行检测而不是针对疾病。找到疾病客观有效的生物标志物将会大大提高诊断率,表 4 是对近 5 年与 COPD 有关的呼出气中一些重要的潜在生物标志物的汇总[40-45]。COPD 的大多数挥发性有机物为醛类或烃类。虽然没有单一的 VOC 可以有效的诊断 COPD,然而多项研究都报导了这三种标志物:hexanal,indole 和 phenol。由于 COPD 病人体内存在氧化应激和脂质过氧化,因此这些代谢物可能与 COPD 病人氧化应激水平升高有关[39]。

表 2 乳腺癌病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Phillips	2003	Nonane Octane,2-methyl Tridecane,5-methyl Undecane,3-methyl Pentadecane,6-methyl Propane,2-methyl
Phillips	2006	Nonadecane,3-methyl Dodecane,4-methyl 2-propanol 2,3-dihydro-1-phenyl-4(1H)-qui isopropyl myristate Nazolinone 1-phenyl-ethanone heptanal
Peng	2010	3,3-dimethyl pentane 2,3,4-trimethyl decane 5-(2-methylpropyl)nonane 2-amino-5-isopropyl-8-methyl-1-azulenecarboni-trile
Mangler	2012	3-methylhexane decene caryophyllene naphthalene Trichlorethylene 6-ethyl-3-octylester 2-trifluoromethyl benzoic acid
Wang	2014	2,5,6-Trimethyloctane 1,4-Dimethoxy-2,3-butanediol Cyclohexanone

表 3 糖尿病病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Minh	2011	Acetone Ethylbenzene Propane Ethanol Methanol
Minh	2012	Acetone Ethylbenzene Xylene Toluene Ethane Pentane Propane Isoprene Ethanol Methanol
Yan	2014	Acetone Xylene Toluene Isopropanol Tridecane Undecane 2,3,4-Trimethylhexane 2,6,8-Trimethyldecane

表 4　慢阻肺病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Westhoff	2010	Cyclohexanone
Westhoff	2011	Indole Menthyl acetate
Bessa	2011	Benzofuran phenol 4-methylanisol 1,2,4-trimethylbenzol
Phillips	2012	Acetic acid Phenol Benzaldehyde Hexanal Benzene Isoprene Nonadecane Toluene Phatalic anhydride Sulphur dioxide
Basanta	2012	Butanoic acid Pentanoic acid Cyclohexanol Dodecanal Hexanal Nonanal Pentadecanal Undecanal 2-pentylfuran Oxirane-dodecyl
Cazzola	2015	2-propanol 1,3,5-tri-tert-butylbenzene Decane 2,4,4-trimethyl-1-pentene Hexyl Butylated hydroxytoluene Limonene Decane,6-ethyl-2 methyl

表 5　哮喘病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Dallinga	2010	Undecane p-xylene Butanoic acid Tridecane 3-(1-methylethyl)-benzene Benzoic acid 1,131″-Ter(cyclopentane) 1-pent-2-one
Caldeira	2011	2,2-dimethylhexane 2,3,6-trimethyldecane Isoprene Acetone 4-methyloctane 2,4-dimethylheptane 2,4-dimethyloctane Tetradecane Decane Dodecane
Caldeira	2012	Decanal Dodecanal Nonanal Isododecane 6-methyl-5-hepten-2-one 3,6-dimethyldecane Decane Dodecane Nonane Tetradecane 1-dodecene
Gahleitner	2013	2-octenal 1-(methylsulfanyl) propane Octadecene 1,4-dichlorobenzene b-Cymene 1,7-dimethylnaphthalene Ethyl-benzene Limonene
Smolinska	2014	2-undecenal Octane 2,2,4-trimethylheptane 2,4-dimethylheptane 2,3,6-trimethyloctane 2,4-dimethylpentane 2-methylhexane 2,6,10-trimethyldodecane 2-methylpentane 2-methylnaphthalene Limonene Biphenyl Acetone

3.2　哮喘与呼出气挥发性标志物　哮喘是一种气道的慢性炎症性疾病,为气道的可逆性阻塞,典型临床症状为喘息,呼吸困难和胸闷[46]。哮喘的一些诊断方法在特异性,灵敏上都存在许多不足。这些病人又常常合并有呼吸系统的其他疾病(如儿童的病毒性感染和老年人的 COPD),这对哮喘的诊断造成了干扰。呼出气中 VOCs 分析可以对气道炎症进行有效的评估,它们主要是由体内活化的白细胞产生 ROS 导致氧化应激而生成,能很好的鉴别哮喘和 COPD 病人[47]。此外还能够区分过敏型和非过敏型哮喘[46]。VOCs 作为炎症通路的标志物还可以指导哮喘病人的个体化治疗。表 5 列出了哮喘中最具鉴别性的 VOCs[48-52]。

4　神经系统性疾病与呼出气挥发性有机化合物

4.1　肌萎缩侧索硬化症与呼出气挥发性标志物肌萎缩侧索硬化症(ALS),是一种进行性的神经系统变性疾病,典型临床症状包括肌无力、肌萎缩、球麻痹以及锥体束征。由于诊断延误、疾病进展迅速、病理改变不可逆等诸多原因,大多数 ALS 病人在出现临床症状后的 2～5 年内死亡,因此确定可靠的诊断标志物,早期诊断,早期干预是有效降低 ALS 病人死亡率的关键性环节。由于肌萎缩侧索硬化症的症状与脊髓型颈椎病(CSM)的症状十分相似,Li 等对这两种疾病的呼出气进行了探索分析,发现了能够鉴别两者的潜在的挥发性生物标志物(表 6),这些化合物在 ALS 组中降低,认为可能与氧化应激,蛋白质聚集,兴奋毒性,线粒体功能障碍,内质网应激以及星形胶质细胞与小胶质细胞的信号通路的改变中的一种或多种机制有关[53]。

表 6　肌萎缩侧索硬化症病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Li	2016	Carbamic acid, monoammonium salt 1-Alanine ethylamide Guanidine, N, N-dimethyl- Phosphonic-acid, (p-hydroxyphenyl)-

4.2　帕金森病与呼出气挥发性标志物　帕金森病(PD)是最常见的神经系统性疾病。目前全世界患有 PD 的占世界人口的 1.6%[54]。这种疾病的诊断主要依赖于临床症状及体征。呼出气分析技术对帕金森病也进行了探索分析(表 7)[54]。PD 与中脑黑质多巴胺能神经元的变形死亡有关,Aluf 发现黑质纹状体多巴胺损伤大鼠模型中氧化应激水平增强[55]。挥发性化合物 Styrene 被认为是与 DNA 损伤有关的毒素,由于氧化应激的增强,PD 病人中的 Styrene 可能会增加,在黑质纹状体多巴胺损伤的大鼠模型中也发现 Styrene 的含量升高[56]。

表 7 PD 病人潜在的呼出气生物标志物

第一作者	时间	潜在标志物
Tisch	2013	Styrene 1-methyl-3-(1-methylethyl) benzene 5-ethyl-2-methyl-octane 2, 3, 6, 7-tetramethyl-octane decamethyl-cyclopentasiloxane Butylated hydroxytoluene ethylbenzene

5 总结

呼出气挥发性有机化合物分析技术是基于血液中代谢的改变进行疾病的检测,而不是基于影像学或者病理形态学,这种技术操作简单,检测结果易于理解。分析单一或一组挥发性标志物可以对病人得临床状况进行评估。同时这种技术与全身循环有关,而不仅仅是针对局部检查的部位,因此有助于克服疾病的异质性。

然而目前呼出气挥发性有机化合物分析技术在临床应用中仍处于起步阶段,同种疾病的挥发性标志物的轮廓图存在很大的差异性。许多标志物的确切代谢机制还不清楚,在研究中,外源性代谢物包括吸入的空气,烟,摄入的食物和药物以及进入体内的其他的外源性分子都会对检测结果造成影响,同时个体间存在的差异性也是我们将面临的挑战,需要更多的研究者们进行深一步的探索。

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(收稿日期:2017-09-05,修回日期:2017-11-12)