

Flatography: Detection of gastrointestinal diseases by faecal gas analysis

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Abstract

Patients presenting with gastro-intestinal symptoms might suffer from a range of possible underlying diseases. An unmet need exists for novel cost-effective,

reproducible, easy-to-perform and non-invasive tests. Hippocrates used body odours to diagnose diseases circa 460 before Christ. The art of diagnostic smelling is making a promising high-tech come-back with portable "electronic diagnostic noses". Analysis of faecal volatile organic compounds is a novel field in metabolomics with considerable potential to improve the diagnosis, phenotyping and monitoring of gastro-intestinal disease. Challenges will be to mature over the coming years by development of a standardized methodology for stool sample collection, storage, handling and analysis. Furthermore, key volatiles need to be identified to improve test accuracy and sensitivity by development of sensors tailored toward the accurate identification of disease specific volatiles. If these challenges are adequately faced, analysis of faecal volatiles has realistic potential to considerably improve screening, diagnosis and disease monitoring for gastro-intestinal diseases.

Key words: Flatography; Electronic nose; Smell; Volatile organic compounds; Gastro-intestinal diseases; Volatile metabolomics

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Core tip: Analysis of faecal volatile organic compounds is a novel field in metabolomics with considerable potential to improve the diagnosis, phenotyping and monitoring of gastro-intestinal disease. Challenges will be to mature over the coming years by development of a standardized methodology for stool sample collection, storage, handling and analysis. Key volatiles need to be identified to improve test accuracy and sensitivity by development of sensors tailored toward the accurate identification of disease specific volatiles. Analysis of faecal volatiles has realistic potential to considerably improve screening, diagnosis and disease monitoring for gastro-intestinal diseases.

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EDITORIAL

Patients presenting with gastro-intestinal symptoms might suffer from a range of possible underlying diseases. Diagnosis and monitoring of disease activity in gastro-intestinal disease (GID) are often time-consuming and carry a high burden on patients and the health care system. Laboratory tests have usually only limited specificity and sensitivity, and endoscopic evaluation of the gastro-intestinal tract is unpleasant and costly. Therefore, an unmet need exists in daily clinical practice for novel cost-effective, reproducible, easy-to-perform and non-invasive tests.

Recent advances in chemical analytical techniques may help to meet these goals. The "Father of Western medicine", the ancient Greek physician Hippocrates, used body odours to diagnose diseases already circa 460 before Christ. Centuries later, the art of diagnostic smelling is making a promising high-tech come-back since portable "electronic diagnostic noses" are currently increasingly studied in medical research setting.

The human body is a metabolic machinery and metabolites, both odorous and non-odorous, are discharged in various bodily excretions, like urine, faeces, blood and breath^[1]. The metabolome is the aggregate of the small molecules (< 2000 Dalton) that form the raw materials of a wide array of metabolic reactions, of both physiologic and pathologic metabolic pathways, and its resulting end products^[2]. Volatile organic compounds (VOCs) are the carbon based end products and in humans up to 1840 different VOCs have been described^[1]. As any disease is characterized by changes in metabolism, these molecules are potential diagnostic biomarkers for a wide range of diseases. This may be especially useful when diseases have clinically similar manifestations, but require different therapeutic approaches.

Analysis of VOCs is a rapid emerging field of basal and clinical research and two basic approaches are used. Firstly chemical analytical techniques, such as gas chromatography linked to mass spectrometry, selected ion flow tube mass spectrometry and ion mobility spectroscopy, help to identify physiochemical properties of the target volatiles in a sample. This can generate valuable insights into the pathophysiology of underlying diseases and the origins of these volatiles. Unfortunately these techniques are relatively cumbersome and costly, thereby limiting their applicability in daily clinical practice, making them primarily suitable as a research tool.

Alternatively VOCs can be analysed by broadly cross-reactive gas-sensor arrays^[3] that employ pattern recognition techniques to discriminate patterns of volatile

biomarkers, so-called smellprints^[4]. The attractiveness of this approach lies in the simultaneous assessment of a full VOC-profile by sensors that are generally low-cost, rapid and suitable as point of care tools. Since such an approach closely mimics mammalian olfaction this technique has been termed an electronic nose (eNose)^[3,5]. This technique does not allow identification of separate compounds, which is generally not a clinical limitation, since determination of individual molecules is mostly not necessary in clinical practice.

Recently published data has shown that analysis of VOCs can discriminate between patients with various diseases, like *Clostridium difficile*, colorectal cancer and inflammatory bowel disease and controls with promising accuracy^[6-11]. On theoretical grounds, VOCs in GID have several metabolic origins. Firstly exogenous, comprising dietary intake and the microbiome, supported by studies showing effect of diet on VOCs/microbiome^[12] and links between VOC and microbiome^[13]. Secondly, local from the primary affected disease site, due to inflammation of mucosa and necrosis, suggested by studies on colorectal cancer^[8] and inflammatory bowel disease^[11]. Thirdly the systemic (immunological) response, such as increased oxidative stress^[14], supported by fact that GI diseases can be detected in breath^[7] and urine^[15].

The composition of the volatile metabolome is highly depended on the analysed substrate. For example, some VOCs found in faeces might be absent in breath^[1]. At least theoretically, VOCs originating from the gastro-intestinal tract dissolve from the intestines into the bloodstream and subsequently being transported to the lungs and might consequently appear in breath. However, some VOCs are chemically unable to dissolve into the bloodstream and some VOCs will be converted by the liver or other organs. Thereby some VOCs will remain or drop below the detection level and in addition new VOCs might be produced or existing VOCs will increase^[1].

Based on the origins of faecal VOCs, analysis of VOCs emanating from faeces, so called flatography, might be the best non-invasive way of diagnosing GID as this substrate offers the most direct and integral reflection of the diseased gastrointestinal tract.

Results of several studies underline that flatography can be used for discrimination of patients with GID^[8,11]. It is an attractive technique from both the patient's and physician's perspective, as the samples can be collected non-invasively. Moreover, in common daily clinical practice, most patients already need to hand in a stool sample for culture, faecal calprotectin or other laboratory tests, therefore collection of an extra sample for faecal gas analysis will take only little effort.

Although published results are promising, this technique is currently still in development and also has some limitations. At this moment, no standard methodology is verified yet. There are no studies available on external validation and also the influences of procedure of stool sampling, storage and handling needs to be sorted out. These development pathways probably require a combination of eNose and chemical analytical techniques

to help identify target VOCs helping to guide the development of primed sensors that are suited for use in clinical practice.

To conclude, analysis of faecal VOCs is a novel field in metabolomics with considerable potential to improve the diagnosis, phenotyping and monitoring of GIT. Challenges will be to mature over the coming years by development of a standardized methodology for stool sample collection, storage, handling and analysis. Furthermore, key volatiles need to be identified to improve test accuracy and sensitivity by development of sensors tailored toward the accurate identification of disease specific volatiles. If these challenges are adequately faced analysis of faecal volatiles has realistic potential to considerably improve screening, diagnosis and disease monitoring for gastro-intestinal diseases.

REFERENCES

- 1 **de Lacy Costello B**, Amann A, Al-Kateb H, Flynn C, Filipiak W, Khalid T, Osborne D, Ratcliffe NM. A review of the volatiles from the healthy human body. *J Breath Res* 2014; **8**: 014001 [PMID: 24421258 DOI: 10.1088/1752-7155/8/1/014001]
- 2 **Wishart DS**, Jewison T, Guo AC, Wilson M, Knox C, Liu Y, Djoumbou Y, Mandal R, Aziat F, Dong E, Bouatra S, Sinelnikov I, Arndt D, Xia J, Liu P, Yallou F, Bjorn Dahl T, Perez-Pineiro R, Eisner R, Allen F, Neveu V, Greiner R, Scalbert A. HMDB 3.0--The Human Metabolome Database in 2013. *Nucleic Acids Res* 2013; **41**: D801-D807 [PMID: 23161693 DOI: 10.1093/nar/gks1065]
- 3 **Persaud K**, Dodd G. Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose. *Nature* 1982; **299**: 352-355 [PMID: 7110356]
- 4 **Röck F**, Barsan N, Weimar U. Electronic nose: current status and future trends. *Chem Rev* 2008; **108**: 705-725 [PMID: 18205411 DOI: 10.1021/cr068121q]
- 5 **Buck L**, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. *Cell* 1991; **65**: 175-187 [PMID: 1840504]
- 6 **Garner CE**, Smith S, de Lacy Costello B, White P, Spencer R, Probert CS, Ratcliffe NM. Volatile organic compounds from feces and their potential for diagnosis of gastrointestinal disease. *FASEB J* 2007; **21**: 1675-1688 [PMID: 17314143]
- 7 **Peng G**, Hakim M, Broza YY, Billan S, Abdah-Bortnyak R, Kuten A, Tisch U, Haick H. Detection of lung, breast, colorectal, and prostate cancers from exhaled breath using a single array of nanosensors. *Br J Cancer* 2010; **103**: 542-551 [PMID: 20648015 DOI: 10.1038/sj.bjc.6605810]
- 8 **de Meij TG**, Larbi IB, van der Schee MP, Lentferink YE, Paff T, Terhaar Sive Droste JS, Mulder CJ, van Bodegraven AA, de Boer NK. Electronic nose can discriminate colorectal carcinoma and advanced adenomas by fecal volatile biomarker analysis: proof of principle study. *Int J Cancer* 2014; **134**: 1132-1138 [PMID: 23959518 DOI: 10.1002/ijc.28446]
- 9 **Arasaradnam RP**, Ouaret N, Thomas MG, Quraishi N, Heatherton E, Nwokolo CU, Bardhan KD, Covington JA. A novel tool for noninvasive diagnosis and tracking of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 999-1003 [PMID: 23478806 DOI: 10.1097/MIB.0b013e3182802b26]
- 10 **Arasaradnam RP**, Quraishi N, Kyrrou I, Nwokolo CU, Joseph M, Kumar S, Bardhan KD, Covington JA. Insights into 'fermentonomics': evaluation of volatile organic compounds (VOCs) in human disease using an electronic 'e-nose'. *J Med Eng Technol* 2011; **35**: 87-91 [PMID: 21204611 DOI: 10.3109/03091902.2010.539770]
- 11 **de Meij TG**, de Boer NK, Benninga MA, Lentferink YE, de Groot EF, van de Velde ME, van Bodegraven AA, van der Schee MP. Faecal gas analysis by electronic nose as novel, non-invasive method for assessment of active and quiescent paediatric inflammatory bowel disease: Proof of principle study. *J Crohns Colitis* 2014 [PMID: 25248313 DOI: 10.1016/j.crohns.2014.09.004]
- 12 **Arasaradnam RP**, Ouaret N, Thomas MG, Gold P, Quraishi MN, Nwokolo CU, Bardhan KD, Covington JA. Evaluation of gut bacterial populations using an electronic e-nose and field asymmetric ion mobility spectrometry: further insights into 'fermentonomics'. *J Med Eng Technol* 2012; **36**: 333-337 [PMID: 22764881 DOI: 10.3109/03091902.2012.690015]
- 13 **Raman M**, Ahmed I, Gillevet PM, Probert CS, Ratcliffe NM, Smith S, Greenwood R, Sikaroodi M, Lam V, Crotty P, Bailey J, Myers RP, Rioux KP. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2013; **11**: 868-75.e1-3 [PMID: 23454028 DOI: 10.1016/j.cgh.2013.02.015]
- 14 **Amann A**, Costello Bde L, Miekisch W, Schubert J, Buszewski B, Pleil J, Ratcliffe N, Risby T. The human volatilome: volatile organic compounds (VOCs) in exhaled breath, skin emanations, urine, feces and saliva. *J Breath Res* 2014; **8**: 034001 [PMID: 24946087 DOI: 10.1088/1752-7155/8/3/034001]
- 15 **Arasaradnam RP**, Westenbrink E, McFarlane MJ, Harbord R, Chambers S, O'Connell N, Bailey C, Nwokolo CU, Bardhan KD, Savage R, Covington JA. Differentiating coeliac disease from irritable bowel syndrome by urinary volatile organic compound analysis--a pilot study. *PLoS One* 2014; **9**: e107312 [PMID: 25330367 DOI: 10.1371/journal.pone.0107312]

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