Interactive CardioVascular and Thoracic Surgery 14 (2012) 511–515
doi:10.1093/icvts/ivr070 Advance Access publication 17 February 2012

Sniffer dogs as part of a bimodal bionic research approach to develop a lung cancer screening[†]

Enole Boedeker, Godehard Friedel and Thorsten Walles*

Department of General Thoracic Surgery, Schillerhoehe Hospital, Gerlingen, Germany

* Corresponding author. Tel: + 49-7156-2032244; fax: + 49-7156-2032003; e-mail: thorsten.walles@klinik-schillerhoehe.de (T. Walles).

Received 11 July 2011; received in revised form 7 October 2011; accepted 13 October 2011

Abstract

Lung cancer (LC) continues to represent a heavy burden for health care systems worldwide. Epidemiological studies predict that its role will increase in the near future. While patient prognosis is strongly associated with tumour stage and early detection of disease, no screening test exists so far. It has been suggested that electronic sensor devices, commonly referred to as 'electronic noses', may be applicable to identify cancer-specific volatile organic compounds in the breath of patients and therefore may represent promising screening technologies. However, three decades of research did not bring forward a clinically applicable device. Here, we propose a new research approach by involving specially trained sniffer dogs into research strategies by making use of their ability to identify LC in the breath sample of patients.

Keywords: Bionic • Breath analysis • Electronic nose • Lung cancer • Review • Sniffer dogs

INTRODUCTION

Lung cancer (LC) represents the second most frequent cancer in men and women with more than 390 000 cases/year in Europe [1]. Among all solid cancers, it is the most common cause of death with an estimated 342 000 deaths/year. The prognosis of LC largely depends on disease discovery at an early stage, when the tumour is still localized [2]. Unfortunately, early LC is not associated with symptoms, and detection therefore is often by chance. Clinical practice has shown that the available diagnostic techniques (such as the various imaging technologies or bronchoscopy including interventional biopsy procedures) have limitations in reliably discriminating between cancer patients and healthy subjects [3, 4]. Very recently, the US American National Lung Screening Trial (NLST), a randomized national trial involving more than 53 000 current and former heavy smokers aged 55–74 years, compared the effects of two screening procedures for LC—low-dose helical computed tomography (CT) and standard chest X-ray—on LC mortality and found 20% lower risk of dying from LC in patients undergoing CT screening [5]. However, currently no screening method is accepted to test for LC.

For almost three decades, research is conducted to develop sensor arrays and pattern recognition technologies, commonly referred to as 'electronic noses' that can detect and recognize odours and flavours [6]. It is hypothesized that these devices may be applicable in identifying volatile organic compounds (VOCs) that are linked to cancers in their early stages and thereby making them potential non-invasive and inexpensive diagnostic tools for the medical community [7, 8]. Since their first delineation by Pauling *et al*. in 1971, 3481 different VOCs have been described in the human breath—most of them in picomolar concentrations (10^{-12} mol/l or particles per trillion) [9, 10]. However, the metabolic origin of tumour-associated VOCs remains speculative [11]. Despite important developments in 'electronic sensing' or 'e-sensing' technologies, their applicability in a clinical setting is limited due to the fact that patients are required to not smoke and to fast before breath samples can be taken. Other limiting factors are that an optimized sample collection is necessary, that the instruments are very sensitive, the long durations for sample analysis, as well as high risks of signal interference. Finally, it has been shown that measuring VOCs with an electronic nose has not yet been standardized and the set-up significantly affects the results. Therefore, it is currently not possible to draw generally accepted conclusions [12].

Offside popular research paths, the medical community's attention is every now and then drawn to the phenomenon that dogs may detect cancer in patients (Table 1). Recently, our group substantiated in a prospective clinical double-blinded trial the ability of specially trained sniffer dogs to identify LC in the breath sample of patients with a sensitivity of 71% and a specificity of 93% [13]. In contrast to e-sensing technologies, the analysis was rapid (<5 s/patient) and interference-free (no influence of smoking, diet, medication, secondary disease). Therefore, dogs seem to be more reliable to identify LC from the breath of patients than the current e-sensing devices. However, it is not clear on what basis (single component, VOC pattern?) the dogs come to a decision. Therefore, we propose a bimodal bionic research approach by combining the state-of-the-art electronic nose technologies and dog training to identify a VOC target for LC screening.

[†]Presented at the 19th European Conference on General Thoracic Surgery, Marseille, France, 5–8 June 2011.

Table 1: Published evidence on the detection of solid tumours by specially trained sniffer dogs

Publication	Year	Type of study	Investigated tumour	Number of tested persons	Substrate	Sensitivity	Specificity
Williams H, Pembroke A. Sniffer dogs in the melanoma clinic? Lancet 1989; 1: 734.	1989	Report of a single case	Malignant melanoma	1	Direct body contact: skin	–	–
Church J, Williams H. Another sniffer dog for the clinic? Lancet 2001; 358: 930.	2001	Report of a single case	Basal cell carcinoma of the skin	1	Direct body contact: skin	–	–
Pickel DP, Manucy GP, Walker DB, Hall SB, Walker JC. Evidence for canine olfactory detection of melanoma. Appl Anim Behav Sci 2004; 89: 107–116.	2004	Prospective study	Malignant melanoma	7	Direct body contact: skin	82%	100%
Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury AJ, Church MRT, Church JCT. Olfactory detection of human bladder cancer by dogs: proof of principle study. BMJ 2004; 329: 712.	2004	Prospective study	Bladder cancer	36 with bladder cancer, 108 without carcinoma (some with cystitis etc.)	Urine	41%	?
Welsh JS. Olfactory detection of human bladder cancer by dogs. Another cancer detected by 'pet scan'. BMJ 2004; 329: 1286–1287.	2004	Report of a single case	Breast cancer	1	Direct body contact: breast	–	–
McCulloch M, Jezierski T, Broffman M, Hubbard A, Turner K, Janecki T. Diagnostic accuracy of canine scent detection in early- and late-stage lung and breast cancers. Interact Canc Ther 2006; 5: 30–9.	2006	Prospective study	LC, breast cancer (BC)	55 with LC/31 with breast cancer/83 healthy	Breath sample	LC: 99%, BC: 88%	LC: 99%, BC: 98%
Gordon RT, Schatz CB, Myers LJ, Kosty M, Gonczy C, Kroener J, Tran M, Kurtzhals P, Heath S, Koziol JA, Arthur N, Gabriel M, Hemping J, Hemping G, Nesbitt S, Tucker-Clark L, Zaayer J. The use of canines in the detection of human cancers. J Altern Complement Med 2008; 14: 61–67.	2008	Prospective study	Prostate cancer, breast cancer	62 with breast cancer/188 healthy persons, 57 with prostate cancer/186 healthy persons	Urine	No better than chance	No better than chance
Horvath G, Järverud GA, Järverud S, Horvath I. Human ovarian carcinomas detected by specific odor. Integr Cancer Ther 2008; 7: 76–80.	2008	Prospective study	Ovarian carcinoma	31 with ovarian carcinoma/? healthy	Tissue specimen	100%	98%
Horvath G, Andersson H, Paulsson G. Characteristic odour in the blood reveals ovarian carcinoma. BMC Cancer 2010; 10: 643.	2010	Prospective study	Ovarian carcinoma	40 with ovarian carcinoma, 4 with endometrial carcinoma, 2 with endocervical carcinoma, 2 with vulvar cancer/? healthy	Tissue specimen (T) and blood serum (B)	T: 100%, B: 100%	T: 95%, B: 98%
Cornu JN, Cancal-Tassin G, Ondet V, Girardet C, Cussenot O. Olfactory detection of prostate cancer by dogs sniffing urine: A step forward to early diagnosis. Eur Urology 2011; 59: 197–201.	2011	Prospective study	Prostate cancer	59 with prostate cancer, 49 with negative prostate biopsy	Urine	91%	91%
Ehmann R, Boedeker E, Friedrich U, Sagert J, Dippon J, Friedel G, Walles T. Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon. Eur Resp J; in press	2011	Prospective study	LC	60 with LC/110 healthy/50 with COPD	Breath sample	71%	93%

Table 2: Strengths and weaknesses of published sniffer dog trials

Publication	Number of dogs	Excluded bias	Limitations
Pickel DP, Manucy GP, Walker DB, Hall SB, Walker JC. Evidence for canine olfactory detection of melanoma. Appl Anim Behav Sci 2004; 89: 107–116.	2		• Low number of study participants • No analysis of possible confounders • Direct body contact: people with phobia of dogs are excluded
Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury AJ, Church MRT, Church JCT. Olfactory detection of human bladder cancer by dogs: proof of principle study. BMJ 2004; 329: 712.	6	• Urine with blood, infection and inflammation was used in control group • Analysis of drugs, menstrual cycle, ethnicity, diet, alcohol consumption, smoking habits, exposure to chemicals, findings on urine analysis	• Only nine cancer samples were tested • Two different training locations • Suppose that dog training was not optimized
McCulloch M, Jezierski T, Broffman M, Hubbard A, Turner K, Janecki T. Diagnostic accuracy of canine scent detection in early- and late-stage lung and breast cancers. Interact Canc Ther 2006; 5: 30–9.	5	• Age of breath sample • Smoking history • Forcefulness of breath during sampling • Concomitant disease: diabetes, dental infection • Diet/most recent meal (garlic, alcohol, coffee, tea, pork, lamb, fish, spicy food)	• Potential confounders: age, smoking behaviour • Breath sampling after biopsy of tumour • Medication and other concomitant diseases were not documented • Repeated use of control samples due to low number of control persons • Same dogs were trained on lung and breast cancer
Gordon RT, Schatz CB, Myers LJ, Kosty M, Gonczy C, Kroener J, Tran M, Kurtzhals P, Heath S, Koziol JA, Arthur N, Gabriel M, Hemping J, Hemping G, Nesbitt S, Tucker-Clark L, Zaayer J. The use of canines in the detection of human cancers. J Altern Complement Med 2008; 14: 61–67.	10	• Medication • Concomitant diseases • Diet/eating and drinking 24 h before testing were documented • For breast cancer samples: deodorants and perfumes were documented	• Urine sampling after biopsy of the tumour • Different dog trainers at different locations, different training methods • Study lasted more than two years → low training intensity • Repeated use of samples for training → dogs eventually recognize the sample and not the cancer specific substance • Inconsistent storage and handling of test samples • No blinding before testing
Horvath G, Järverud GA, Järverud S, Horvath I. Human ovarian carcinomas detected by specific odor. Integr Cancer Ther 2008; 7: 76–80.	1	• Differentiation against other gynaecological tumours • Differentiation against other non malignant tissue of the same individual • Tumour stage	• Medication not analysed • Concomitant disease not analysed • Diet not analysed
Horvath G, Andersson H, Paulsson G. Characteristic odour in the blood reveals ovarian carcinoma. BMC Cancer 2010; 10: 643.	2		• Medication not analysed • Concomitant disease not analysed • Diet not analysed
Cornu JN, Cancal-Tassin G, Ondet V, Girardet C, Cussenot O. Olfactory detection of prostate cancer by dogs sniffing urine: A step forward to early diagnosis. Eur Urology 2011; 59: 197–201.	1	• No correlation with age, height, weight, PSA level, result of digital rectal examination	• Medication not analysed • Concomitant disease not analysed • Diet not analysed • False-negative prostate cancer patients in control group
Ehmann R, Boedeker E, Friedrich U, Sagert J, Dippon J, Friedel G, Walles T. Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon. Eur Resp J; in press	4	• Excluded as confounders: age of breath sample, biopsy before or after breath sampling, age of study participants, sex, body mass index, smoking habits, lung function parameters, concomitant diseases • Chronic obstructive lung disease did not influence test results	• Training effect during testing → dog training potentially not optimized

CONCEPT

The search for a VOC that is specific for LC and represents a suitable target for LC screening means looking for a needle in a haystack: So far, more than 3400 VOCs have been identified in human breath samples [7]. It can be hypothesized that a fraction of them accompany certain pathological conditions or diseases like LC. Unfortunately, the majority of VOC signals probably are detectable in the breath of every individual, independent of his or her health condition. Therefore, research faces a dual challenge: (i) identifying all VOCs and characterizing their biochemical composition and (ii) assigning identified VOCs to pathological conditions and diseases. The former requires highly sensitive absorber materials and sensor technologies covering the entire range of VOCs, whereas the latter requires neural networks for pattern recognition. While optimized e-sensing technologies may be able to address the first challenge, specially trained dogs may be of use for the second. Narrowly defined patient populations (for instance healthy non-smokers, confirmed LC or chronic obstructive pulmonary disease (COPD) of different disease stages, benign lung lesions and metastatic lung disease) tested by both research approaches may open the door to encircle potential VOCs that may be interesting for LC screening.

DISCUSSION

LC continues to represent a heavy burden for health care systems worldwide. Epidemiologic studies predict that its role will increase in the near future [14]. While patient prognosis is strongly associated with tumour stage and early detection of disease, no screening test exists so far. Acknowledging the existing limitations of current analytical tools, not walking along the beaten track, may be worthwhile to identify an applicable screening test for LC.

'Bionics' is the transfer of biological methods and systems found in nature to the study and design of engineering systems and modern technology [15]. Examples for the successful transfer of technology are (i) the development of dirt- and water-repellent paint (coating) from the observation that the surface of the lotus flower plant is practically unsticky for anything (the lotus effect); (ii) the hulls of boats imitating the thick skin of dolphins; (iii) sonar, radar and medical ultrasound imaging imitating the echolocation of bats [15]. The outstanding sensitivity of the canine olfactory system has been acknowledged by using sniffer dogs in military and civilian service for the detection of a variety of odours. So, why not using them for the detection of LC?

A PubMed search (limited to 'human species' and publications in German on English) for the terms 'sniffer dogs and cancer' (5 results), 'canine scent detection' (13 results) and 'canine olfaction' (70 results) followed by an analysis of the identified studies ultimately provides three case reports and eight studies reporting on the phenomenon of specially trained sniffer dogs identifying solid tumours in patients (Table 1). Collectively, 449 patients with skin tumours ($n = 9$), or bladder ($n = 36$), breast ($n = 94$), lung ($n = 115$), prostate ($n = 116$), ovarian ($n = 71$), and other solid cancers ($n = 8$) have been tested. Unfortunately, most findings have to be questioned due to numerous imitations in the study design and data analysis (Table 2). However, a recent study specifically addressed the existing shortcomings and documented a moderate sensitivity (71%) and high specificity (93%) for specially trained sniffer dogs to indentify LC from a breath sample of patients [13]. This analysis confirms the existence of a stable marker (or scent pattern) that is strongly associated with LC and independent from COPD, but can be reliably discriminated from tobacco smoke, food odours and potential drug metabolites. Future studies of similar design are necessary to assess whether this dog indication is specific for LC or whether it is linked to the presence of any form of cancer (in the lung). To be applicable as a clinical screening test in patients with pathological chest CT findings, it has to be tested whether sniffer dogs can discriminate benign lung lesions from LC.

By combining highly sophisticated e-sensing technologies in the analysis of breath samples of carefully defined patient populations that have been characterized by predating sniffer dog testing for being positive or negative for (a so far unknown) LC marker, the goal to identify a LC-specific VOC may be accomplished (earlier).

Funding

This research was funded by internal research funds of the Robert-Bosch-Krankenhaus, Stuttgart (Innovationsfond RBK "Das forschende Krankenhaus" KKF-11-5).

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr. L. Molins (*Barcelona, Spain*): It is a surprising abstract and a perfect demonstration that dogs are perhaps more clever than electronic noses. We are impressed with those results and we are trying to do something like that, perhaps to include it in a screening program. That is the question that I would like to ask you, first of all, if you are going to compare the electronic noses with different sniffer dogs and then if you think it could in the future be included in a screening program?

Dr. Boedeker: We don't have plans yet to compare electronic diagnosis with a dog at the moment. The next thing we would like to test is if they can tell the difference between lung cancer and other kinds of cancer. But I think using dogs as a screening tool is a problem, it is not so easy, because it is quite hard to train the dogs, to tell them what they should sniff. It is difficult because you don't have a pure substance to train with, as you have with drugs or other things, but with cancer you don't have the substance. So you need a lot of samples just for the training and also to keep the dogs fit afterwards. They are living creatures and they are not always reliable every day. I think in the end, machines or devices have to take over this. But maybe with further research the dog can help us to find a screening method for lung cancer.

Dr. F. Detterbeck (*New Haven, CT*): I have a question about the patients that had lung cancer. Do you have information about the size of lung cancer, what stage of lung cancer they had? That would be potentially important if we address the screening question. If all of these patients had fairly advanced cancer, then that may be less useful than if they had very tiny cancers.

Dr. Boedeker: It is difficult to tell statistically with our numbers, because more than half of the patients had higher lung cancer stages, and this is also because we had to find enough samples, and most people who come to the hospital have higher stages of lung cancer. But as was seen, there was no difference between low and high stages of lung cancer.

Dr. A. End (*Vienna, Austria*): Do you think that the dogs need permanent training to keep their ability?

Dr. Boedeker: I think at least every few weeks, months, they need training to keep their ability. And now we work on a reward-based method, and it was double-blinded, but still the dogs were rewarded for what they did, because in the end, someone knew which was the right sample. But then you would have to train the dogs in a different way. They indicate the cancer and you don't know if they are right or not, so you can't give them a reward. You can only give them a reward if you know the answer.

Dr. End: How much does a dog cost? What is the price?

Dr. Boedeker: I don't know, I didn't calculate it, because all of the people who worked on this project did it voluntarily and the dog owners just had fun doing this. Everybody did their job voluntarily this time.