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EDITORIAL

Adaptive servo-ventilation for central sleep apnea: What are the lessons learned?

Heart failure remains a major health challenge despite advancements in medical therapy.[1] Patients with heart failure with reduced ejection fraction (HFrEF) often develop a form of central sleep apnoea (CSA) characterized by recurrent central apnoeas and hypopnoeas interposed by a prolonged crescendo -decrescendo pattern of ventilation, known as Cheyne-Stokes respiration (CSR).[2] Although CSR with CSA (CSR-CSA) is common among patients with HFrEF, it is now clear that obstructive sleep apnoea (OSA) is even more common in such patients.[3] In patients with HFrEF, OSA often presents with a prolonged crescendo-decrescendo pattern of breathing resembling CSR-CSA but with obstructive, rather than central respiratory events.[3] The common underlying cause of this sculpted CSR pattern is lower than normal cardiac output, with prolonged time for changes in PaO_2 and $PaCO_2$ in the lungs during respiratory events to reach the peripheral and central chemoreceptors to stimulate breathing. One of the reasons why both CSA and OSA are more common in patients with HFrEF than in the general population is fluid retention. When upright, patients with HFrEF accumulate fluid in their legs, so that when lying down to sleep at night, gravitation causes some of this fluid to shift to the upper body. If fluid accumulates mainly in the lungs, CSA may emerge due to stimulation of pulmonary vagal irritant receptors provoking hyperventilation that drives $PaCO_2$ below the apnoea threshold. If fluid collects mainly in the neck it may increase peripharyngeal tissue pressure causing the pharynx to narrow, thus predisposing to obstructive events.[4]

Unfortunately, current standard full polysomnography (PSG) may fall short in distinguishing central from obstructive events for at least three reasons. A). While oesophageal pressure detects effort, standard PSG belts detect thoracic and abdominal movements. In apnoeas where upper airway obstruction is present, but thoraco-abdominal motion is subtle, and not obviously out-of-phase, it may be difficult to distinguish such obstructive events from central events in patients with HFrEF. In addition, nasal pressure is not helpful in distinguishing obstructive from central apnoeas because, in either case, there is no signal. B) In most patients with HFrEF, and either CSA or OSA, hypopnoeas rather than apnoeas predominate. Differentiating obstructive from central hypopnoeas is more difficult than classifying apnoeas because thoraco-abdominal motion is present but may not be obviously out-of-phase. Similarly, nasal pressure tracings may not clearly demonstrate flattening as a sign of airflow limitation in the presence of upper airway obstruction. C) Patients with HFrEF may convert from mainly obstructive to mainly central events over a single night due to an overnight decrease in cardiac output, increased lung to chemoreceptor circulation time, and a fall in $PaCO_2$ below the apnoea threshold.[5]

While continuous positive airway pressure (CPAP) is able to abolish OSA, the treatment of CSR-CSA is more challenging. The first large multicenter randomized trial (CANPAP), that evaluated the impact of CPAP in patients with HFeEF and CSR-CSA on a hard endpoint (cardiovascular morbidity and mortality) was neutral.[6] One of the reasons may have been that CPAP only reduced the apnoea-hypopnoea index (AHI) by about 55%. However, a subsequent post hoc analysis suggested a protective effect of CPAP among the sub-group of patients in whom the AHI fell below 15 events/hour while on CPAP.[7]

Adaptive servo-ventilation (ASV) was designed to abolish CSR-CSA by providing variable levels of inspiratory pressure support to counteract decreases or cessation of tidal volume during central hypopnoeas and apnoeas.[8] Essentially, ASV stabilizes breathing by providing pressure support that is a mirror image of the patient's respiratory drive. Adaptive servo-ventilation can be triggered by decrease in minute ventilation, in the case of the original ResMed devices (ASVmv), or peak flow (ASVpf), in the case of the Philips devices. A consistent literature showing the beneficial effects of ASV in patients with HFrEF and CSR-CSA on physiological variables[8,9] justified the next step.

The SERVE-HF trial[10] was the largest multicenter randomized trial designed to test the hypothesis that treating CSR-CSA by ASVmv in patients with HFrEF would reduce the rate

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of the primary composite endpoint: the first event of death from any cause, life-saving cardiovascular intervention, or unplanned hospital admission due to worsening of HF. After a median follow-up of 31 months, the primary outcome was neutral. However, ASVmv induced an increase in all-cause and cardiovascular mortality. In addition, the safety of ongoing studies testing the treatment of CSR-CSA with other forms of ASV, such as ASVpf, was questioned.[11-13]

In this issue of Pulmonology, a statement[14] by the Portuguese Society of Pulmonology and the Portuguese Sleep Association sheds light on this topic by trying to separate the wheat from the chaff. The Portuguese Task Force states that the prescription of ASV plunged after the SERVE-HF publication. SERVE-HF had multiple study design problems that have been described by the Portuguese Task Force and debated in several editorials.[11-13] The Portuguese Task Force[14] raises an important flag by pointing out that ASVmv used in SERVE-HF has a minimum pressure support of 3 cm H_2O on a background minimum expiratory pressure of 5 cm H_2O, even when the patient Is hyperventilating, that may accentuate hyperventilation and be harmful to the patients by amplifying alkalosis related to use of diuretics. If potassium levels are also low, this could facilitate development of malignant cardiac arrhythmias. Another critical point was that the study was over interpreted. SERVE-HF was powered to answer a specific question, and the main result was neutral. SERVE-HF had a large number of secondary endpoints. Regulatory agencies, industry and medical societies, however, have taken a conservative approach, and stated that ASV increases cardiovascular mortality, based on this secondary endpoint.[10] One argument in favor of this approach is that increased cardiovascular mortality is not a trivial secondary endpoint. However, statistics must be interpreted with caution. For instance, the rate of antiarrhythmic drug use at study entry was significantly higher in the ASV group than in the control group (P=0.005) and the excess mortality in the ASVmv treated group was likely due to sudden cardiac death.[10,15] Despite the low p value, this difference must be interpreted with caution as it was not driven by a hypothesis.

In contrast to SERVE-HF, that only recruited patients that were classified as having CSA, the ADVENT-HF trial[16] is a large multicenter randomized trial that was designed to test the impact of the treatment of both OSA and CSA in patients with HFrEF. Unfortunately, after the results of the SERVE-HF trial were published in 2015, regulatory agencies in Germany and France prohibited the ADVENT-HF trial to continue to recruit patients with CSA in their countries. This was a regrettable decision for the following reasons. First, it overruled the data and safety monitoring committee that regularly reviewed outcomes data and clearly stated that there was no discernable safety signal. Second, it caused a significant decrease in recruitment of patients with CSA into the trial, reducing overall enrolment. Third, while the fear of harming patients is legitimate for clinical practice, clinical trials are designed to answer difficult clinical questions. Moreover, the device used in ADVENT-HF differed from that used in SERVE-HF as it is peak flow-triggered with lower default inspiratory and expiratory pressure settings. While the field waits for the final results of ADVENT-HF, it is important to keep clinical practice on track. Adaptive servo-ventilation is still recommended in other settings, for instance among patients with CSA who have heart failure with preserved ejection fraction, or those with idiopathic CSA or CPAP-emergent CSA. In this context, the Portuguese society has taken a step forward and proposed algorithms on how to manage patients with CSA.

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EDITORIAL

What have we learnt from Covid-19 Pandemia? Looking to the future

More than two and a half years ago, the World Health Organization (WHO) declared COVID-19 a pandemic. Since then, more than six million lives worldwide have been lost to the disease, and daily life has been disrupted in countless ways. Some countries are returning to a degree of normality, although the threat of another wave of disease induced by a variant virus remains. The consequences that Covid-19 is producing over time are becoming known and documented, in addition to the effects that SARS-CoV-2 produces on the previous pathology of patients.[1,2] We reflect on five points the world has learned through the course of the pandemic.

1. Infectious disease and economics. Economic impact: The direct health impact may not be what we remember most. The indirect effects on the health of the population, as a result of delayed care, overburdened health systems and the increased burden of mental health, are significant. Children, especially those from low-income families, suffered significant and untold damage during prolonged school closures. The economic damage and dislocation caused by the pandemic have diminished the quality of life for people around the world.[3,4] We learn from challenges, disruption and failure.
2. The clinical presentation and outcomes of acute COVID-19 are well described. Most patients have mild disease and only a minority need hospital admission. In most cases, patients experience a complete resolution of their symptoms after 2 to 6 weeks, but a subgroup present long lasting symptoms.[5] Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of COVID-19 with symptoms; these last for at least two months and cannot be explained by an alternative diagnosis.[6,7] Some authors[8] have proposed the following integrative classification for post-COVID symptoms: potentially infection related-symptoms (up to 4—5 weeks), acute post-COVID symptoms (from week 5 to week 12), long post-COVID symptoms (from week 12 to week 24), and persistent post-COVID symptoms (lasting more than 24 weeks). An additional clinical problem has been the effect of the Covid-19 infection on patient́s pre-existing pathologies which can worsen.[2] Indeed, COVID-19 can affect the respiratory system in a variety of ways and across a spectrum of levels of disease severity, depending on a person's immune system, age and comorbidities.[2] We have learnt that a global public health effort is required to increase awareness about minimizing the burden of the comorbidity conditions that cause fatalities in COVID-19 infected peoples. The pandemic has bluntly challenged us; our response has evolved as new information and tools have become available. Emerging evidence, on topics such as the benefits of masking, the possibility of repeat infection, the risk of new variants, the difficulty of achieving herd immunity, and the benefits of boosters, has required changes in policy and behaviour.[9,10] For example, some studies have suggested that respiratory protection and social distancing reduced by over 50% of the number and severity of COPD and bronchiectasis exacerbations and by even more the number of seasonal flu infections. Although these results should be confirmed by prospective controlled studies, it seems obvious that masking, among other protective actions, at least during the winter period could be a very cost-effective measure among susceptible patients with chronic airways diseases.[11] Governments, healthcare and businesses have had to weigh the benefits of incorporating new evidence into their response plans against the confusion and frustration caused by frequent change. Agility in investigation, decision-making, and strong communications have enabled the crisis to be responded to more effectively.
3. The vaccine development paradigm has been transformed. Two and a half years later, it is easy to forget how remarkable the development of COVID-19 vaccines was. Moving in just one year from a genomic sequence to the authorization of a COVID-19 vaccine shattered all previous records. In addition, biomedical science delivered multiple vaccines with high efficacy against severe COVID-19 and a strong overall safety profile.[12]

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Conversely, weaknesses in vaccine manufacturing and equitable distribution require change: there have been persistent inequalities in access, it is important to increase the global vaccine-manufacturing capacity for emergencies because it would help ensure rapid access for the greatest number of people. Low-income regions have to develop their own local capacity so that they depend less on global agreements and long supply chains. Trust is one of the most delicate but critical requirements for an effective pandemic response. In some countries there has existed vaccine scepticism and that has limited the demand. Trust is hard to manufacture during a crisis. Building confidence in specific areas (including biomedical science) can be especially important.[13,14] Around the world, a significant part of the population declined to take the vaccine and probably that helped SARS-CoV-2 to mutate and spread.

4. Life after Covid-19 has changed. Are the same number of workers required at the present time? How many of those who currently work can do so from home? What influences has this had on companies and states? Covid-19 affected employment and the main concern now for all countries is high inflation rates.[15] These are questions that at the present time are not fully answered and that will have to be resolved in the future. Two years and a half on, the facts are clear: no country kept its economy moving well without controlling the spread of the virus as well. On the other hand, and is clear that it was necessary for the schools to be closed and teaching to begin online, which proved to be "a poor substitute" for classrooms. Likewise, and especially in the first waves of the pandemic, hospitals and primary care services had to adapted to the demands of the request for services (creation of areas in primary care to segregate patients suspected or confirmed to have COVID-19, implementation of telephone consultations, identifying additional space, ensuring sufficient personnel, cancelling elective surgeries, discharging stable patients immediately, maintaining line of sight, minding the air, availability of protective equipment, use of technology to connect families, maintaining caches of supplies and diversify supply chains, ...).[16]
5. In the area of scientific publications, this pandemic has conditioned an urgent need to acquire and disseminate knowledge that can quickly reach all specialists and that can contribute to improving preventive and therapeutic aspects. In this rush to publish, without a doubt, "quality" has been sacrificed to "need", with a share of "opportunity". In the early days of the pandemic, most of the investigation research articles could be considered at risk of bias, with few studies adhering to good standards of reporting.[17] Some authors have found that the majority of Covid-19 research is composed of publications without original data, high risk of bias, a limited number of patients and an alarmingly high rate of retraction.[18,19] We need a balance between the velocity and quality of research, and to carefully consider medical information and clinical applicability in a pressing pandemic context. Publishing of research works should proceed with rigor and this is the collective responsibility of researchers and publishers alike.

We have learned from our previous mistakes, but in a pandemic like the one we living through we have to be more supportive, justify collective action in the face of a common threat, be more proactive, we should regard COVID-19 as a training run for something that could be much worse, and organize our governance, global interactions, institutions and practices accordingly. What we must not do is to blame one another in this time of uncertainty. Until every country is safe, no country will be safe.

Author's contribution

JIG-O: writing the core content of the study and revising it critically for important intellectual content. MAM-G: critical review of the manuscript. All authors approve the current version of the manuscript.

Conflicts of interest

JIG-O has received honoraria for lecturing, scientific advice, participation in clinical studies or writing for publications for the following (alphabetical order): Aflofarm, AstraZeneca, Chiesi, Esteve, Faes, Gebro, Menarini, and Pfizer. MAM-G have received grants from Vitalaire and Phillips and Fees from Astra-Zeneca, GSK, Grifols, Zambon, TEVA and Chiesi

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ORIGINAL ARTICLE

The function of miR-637 in non-small cell lung cancer progression and prognosis

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Abstract
Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer with a high mortality rate and poor prognosis. miR-637 has been reported to regulate tumor progression and act as a prognosis biomarker of various cancers. Its functional role in NSCLC was investigated in this study.
Methods: The expression level of miR-637 in NSCLC tissues and adjacent normal tissues of 123 NSCLC patients was analyzed by qRT-PCR. The association between miR-637 and clinical pathological features in the prognosis of patients was analyzed. Cell transfection was performed to overexpress or knockdown miR-637 in H1299 and HCC827. The proliferation, migration, and invasion of H1299 and HCC827 were evaluated by CCK8 and Transwell assay.
Results: miR-637 expression was significantly decreased in NSCLC tissues and cell lines relative to normal tissues and cells. The survival rate of NSCLC patients with low miR-637 expression was lower than that of patients with high miR-637 expression. Additionally, miR-637 served as a tumor suppressor that inhibited cell proliferation, migration, and invasion of NSCLC.
Conclusion: Downregulation of miR-637 in NSCLC was associated with TNM stage and poor prognosis of patients and served as a tumor suppressor in NSCLC. These results provide a potential strategy to control NSCLC.

Introduction

Non-small cell lung cancer (NSCLC) accounts for most cases of lung cancer; it is one of the most frequently diagnosed cancers and the leading cause of cancer-related death.[1] In clinics, the majority of NSCLC cases have developed to the middle or advanced stage when specific symptoms are apparent, which results in the high mortality rate.[2,3] Tumor metastasis, recurrence, and treatment failures are the main factors responsible for the poor prognosis of NSCLC.[4,5]. Despite the great improvement in the diagnostic and therapeutic strategies of NSCLC in the past decades, the 5-year overall survival rate of NSCLC was still lower than many other cancers. Thus, there is a need for more efficient strategies to improve the prognosis and therapy for patients with NSCLC.

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MicroRNAs (miRNAs) are endogenous conserved non-coding RNAs, which can regulate mRNA translation and stability by binding 3′UTR of targets.[6,7] Research has shown that miRNA is involved in almost the whole process of tumor occurrence and development. Recently, with the development of molecular biology evidence suggested the modulator role of miRNAs in the differentiation, proliferation, apoptosis, and progression of several cancers.[8,9] MiR-340−5p was identified as tumor promoter of thyroid cancer, which promoted thyroid cancer proliferation by inhibiting BMP4.[10] miR-153 was considered a prognostic biomarker of prostate cancer, as its upregulation predicates the poor prognosis of patients.[11] In NSCLC, downregulated miR-940 has been demonstrated to suppress tumor progression and is associated with poor survival rate of NSCLC patients.[12] MiR-512−5p, miR-191, miR-1247, and many other miRNAs have been reported as playing vital roles in the progression and prognosis of NSCLC.[13-15] miR-637 is identified as a downregulated miRNA in NSCLC and has been reported to affect the development of various cancers.[16] For example, miR-637 was found to be correlated with poor prognosis of glioma and its downregulation could promote tumor cell migration and invasion.[17] Moreover, it is also involved in the progression of hepatocellular carcinoma, melanoma, pancreatic ductal carcinoma, and cholangiocarcinoma.[18-21] Therefore, the dysregulation of miR-637 might also act as a biomarker for the progression and prognosis of NSCLC. To verify this hypothesis, we investigated the expression and function of miR-637 in NSCLC tissues and cells by a series of *in vitro* experiments, aimed to provide more references for the treatment and management of NSCLC.

Materials and methods

Patients

NSCLC tissues and adjacent normal tissues of 123 patients with NSCLC were collected during surgery. Patients were recruited from January 2011 to December 2013, which were diagnosed and confirmed with NSCLC at Binzhou Medical University Hospital. All patients had never received any other treatments before surgery. All patients signed informed consent and were followed up for 5 years to obtain the survival information. Collected tissues were confirmed with pathology diagnosis following the International Union against Cancer (UICC) and frozen in liquid nitrogen and stored at −80 °C for the following experiments. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Binzhou Medical University Hospital (NO.: 20101201) and individual consent for this retrospective analysis was waived.

Cell culture and transfection

H1299, HCC827, H1755, and A549 and normal lung epithelial cell BEAS-2B were purchased from ATCC. All cells were cultured in DMEM culture medium with 10% fetal bovine serum (FBS) at 37 °C in a humidified incubator with 5% CO_2.

Transfection of miR-637 mimic, miR-637 inhibitor and corresponding negative control (mimic NC and inhibitor NC) (RiboBio, Guangzhou, China) into NSCLC cells was performed with a concentration of 50 nM to regulate the expression of miR-637. Transfection was conducted with the Lipofectamine 2000 Reagent (Invitrogen, USA) following the manufacturer's instructions and evaluated by the expression of miR-637 after transfection for 48 h. Untreated cells were used as mock group.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was first extracted from collected tissues and cell lines with the TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Then cDNA was synthesized using a microRNA reverse transcription kit (Applied Biosystems, Foster City, USA). Finally, qRT-PCR was performed to detect the expression of miR-637 with the SYBR Green I Master Mix kit (Invitrogen) and the 7300 Real-Time PCR System (Applied Biosystems, USA). miR-637 expression normalized by U6 and calculated by the $2^{-\Delta\Delta Ct}$ method.[22]. The thermocycling conditions were as follow: 95 °C for 5 min, 40 cycles of 95 °C for 10 s, 60 °C for 20 s, and 72 °C for 10 s, and then final extension at 72 °C for 5 min.

CCK8 assay

Transfected cells were added to the 96-well plates at a density of 5×10^3 cells per well and cultured for 24 h, 48 h, 72 h. At the appropriate time points, CCK8 reagent was added to each well and further incubated for 4 h at 37 °C with 5% CO_2. Finally, the absorbance of each well at 450 nm was measured by a microplate reader (Thermo Fisher Scientific).

Transwell assay

1×10^5 cells were seeded into the upper chamber of 24-well transwell chambers (8 μm pore size, Multiskan MK3, Thermo, Waltham, MA, USA) incubated with culture medium without FBS at 37 °C for 24 h. In the bottom chamber, the culture medium with 10% FBS was added as a chemoattractant. For the invasion assay, the Matrigel (BD Biosciences, Franklin Lakes, NJ, USA) was added into the upper chamber before seeding cells. The plates were incubated at 37 °C for 48 h, then, migrated and invasive cells were stained with 0.1% crystal violet and counted by a microscope. The number of migrated and invasive cells was obtained from five representative field and calculated the mean value.

Statistical analysis

Data were presented as mean ± standard deviation (SD) and analyzed by SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5.0 software (GraphPad Software, Inc., Chicago, USA). Comparison between groups was conducted by paired Student's *t*-test and one-way ANOVA followed Turkey test. Kaplan-Meier analysis and Cox regression analysis were used to plot the survival curves of patients and evaluate the

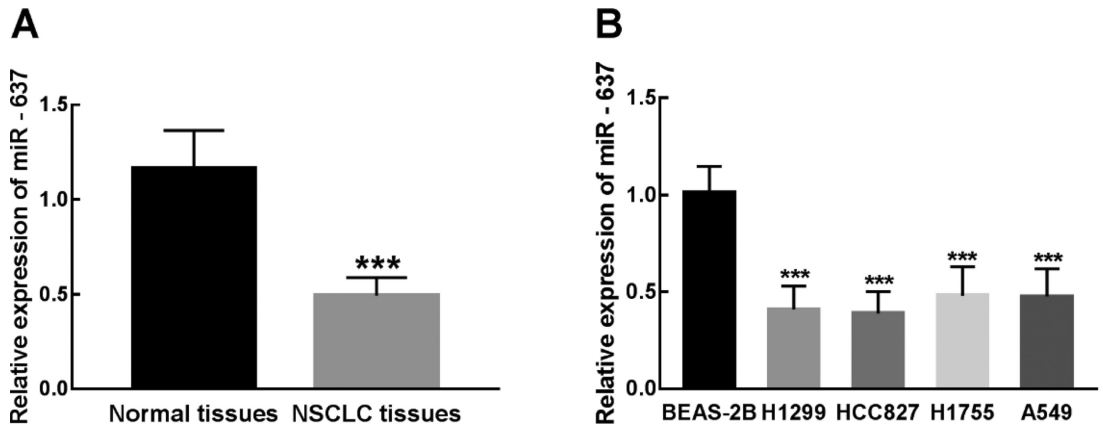

Figure 1 The expression level of miR-637 in NSCLC. **A.** The expression level of miR-637 in NSCLC tissues and adjacent normal tissues. ***$P < 0.001$. **B.** The expression of miR-637 in NSCLC cell lines (H1299, HCC827, H1755, and A549) and normal epithelial cell BEAS-2B ***$P < 0.001$.

prognostic value of miR-637. *P* value less than 0.05 was considered statistically significant.

Results

miR-637 was significantly downregulated in NSCLC tissues and cell lines

The results of qRT-PCR showed that relative expression of miR-637 in 123 collected NSCLC tissues significantly decreased in comparison with that in adjacent normal tissues ($P < 0.001$, Figure 1**A**). The downregulation of miR-637 was also found in NSCLC cells (H1299, HCC827, H1755, and A549) relative to the expression in the normal lung epithelial cell BEAS-2B ($P < 0.001$, Figure 1**B**). The dysregulation of miR-637 indicated its potential biomarker role in the prognosis and progression of NSCLC.

miR-637 was associated with the disease progression in NSCLC patients

Association between miR-637 expression level in NSCLC and the clinical and pathological features of patients was

Table 1 Patients' clinical features and their association with miR-637 expression.

Patient clinical features	Patients ($n = 123$)	Expression of miR-637		*P* value
		Low ($n = 71$)	High ($n = 52$)	
Age (years)				0.604
≤ 60	53 (43.09%)	32 (60.38%)	21 (39.62%)	
> 60	70 (56.91%)	39 (55.71%)	31 (44.29%)	
Gender				0.394
Male	74 (60.16%)	45 (60.81%)	29 (39.19%)	
Female	49 (39.84%)	26 (53.06%)	23 (46.94%)	
Differentiation				0.180
Well and moderate	77 (62.60%)	48 (62.34%)	29 (37.66%)	
Poor	46 (37.40%)	23 (50.00%)	23 (50.00%)	
Tumor size (cm)				0.101
≤ 5	65 (52.85%)	42 (64.62%)	23 (35.38%)	
> 5	58 (47.15%)	29 (50.00%)	29 (50.00%)	
Lymph node metastasis				0.187
Negative	72 (58.54%)	38 (52.78%)	34 (47.22%)	
Positive	51 (41.46%)	33 (64.71%)	18 (35.29%)	
TNM stage				0.031
I-II	84 (68.29%)	54 (64.29%)	30 (35.71%)	
III-IV	39 (31.71%)	17 (43.59%)	22 (56.41%)	
Histology				0.320
Adenocarcinoma	57 (46.34%)	36 (63.16%)	21 (36.84%)	
Squamous cell carcinoma	45 (36.59%)	22 (48.89%)	23 (51.11%)	
Large cell carcinoma	21 (17.07%)	13 (61.90%)	8 (38.10%)	

TNM: Tumor Node Metastasis.

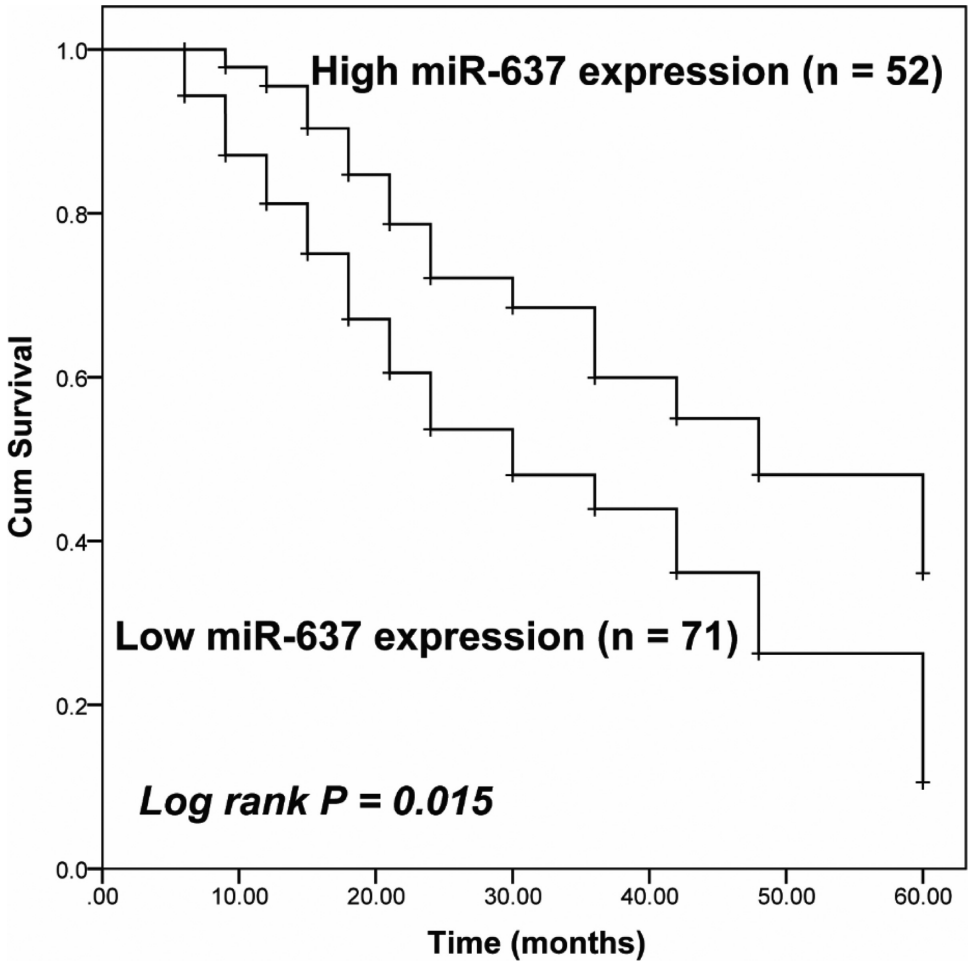

Figure 2 Kaplan-Meier curve of patients based on the expression of miR-637 in NSCLC tissues.

evaluated. The average expression level of miR-637 in NSCLC tissues 0.493 was used as the cut-off to divide 123 patients into two groups, including a low miR-637 expression group contains 71 patients and a high miR-637 expression group contains 52 patients. The χ^2 test showed that the expression of miR-637 was significantly associated with the TNM stage of patients ($P = 0.031$), while other features, such as age, gender, differentiation, tumor size, lymph node metastasis, and histology showed no significant association ($P > 0.05$, Table 1).

miR-637 was an independent prognostic indicator of NSCLC patients

Considering the significant association between miR-637 expression and the TNM stage of patients, it was speculated that the downregulation of miR-637 might affect the prognosis of patients. The survival of NSCLC patients was plotted by the Kaplan-Meier method and compared by the log-rank test shown in Figure 2. The decreased expression level of miR-637 was associated with the poor prognosis of NSCLC patients (Log-rank $P = 0.015$). Additionally, by Cox regression analysis, miR-637 (HR value = 2.234, 95% CI = 1.203−4.149, $P = 0.011$) and TNM stage (HR value =1.805, 95% CI = 1.026−3.175, P value = 0.040) were considered as two independent risk factors for the prognosis of NSCLC patients (Table 2).

miR-637 suppressed cell proliferation of NSCLC

miR-637 was overexpressed or knockdown in H1299 and HCC827 by the transfection of miR-637 mimic or miR-637 inhibitor. The expression level of miR-637 was significantly increased in miR-637 mimic treated cells and decreased in miR-637 inhibitor-treated cells, which indicated the transfection was successful for the following experiments ($P < 0.001$, Figure 3**A**).

Next, the proliferation ability of transfected cells was evaluated by CCK8 assay. After the transfection of miR-637 mimic, the proliferation of H1299 and HCC827 was significantly inhibited by the overexpression of miR-637 ($P < 0.05$, Figure 3**B**). On the contrary, the downregulation of miR-637 by the transfection of miR-637 inhibitor dramatically promoted NSCLC cell proliferation ($P < 0.05$, $P < 0.01$, Figure 3**B**).

miR-637 inhibited cell migration and invasion of NSCLC

The results of Transwell assay showed that the number of migrated and invasive cells significantly decreased in

Table 2 Association between survival rate of patient and patients' clinical features by Cox regression analysis.

	HR factor	95% CI	*P* value
miR-637	2.234	1.203—4.149	0.011
Age	1.136	0.665—1.941	0.640
Gender	1.214	0.700—2.106	0.490
Differentiation	1.366	0.768—2.430	0.288
Tumor size	1.456	0.826—2.566	0.194
Lymph node metastasis	1.687	0.917—3.104	0.092
TNM stage	1.805	1.026—3.175	0.040
Histology	1.426	0.658—3.092	0.368

TNM: Tumor Node Metastasis.

H1299 and HCC827 after miR-637 mimic transfection, while miR-637 inhibitor promoted cell migration and invasion, indicating the inhibitor role of miR-637 in cell migration and invasion of NSCLC ($P < 0.001$, Figure 4**A and B**).

Discussion

NSCLC is the most common pathological type of lung cancer and has been linked to poor prognosis with a bad 5-year survival rate.[23,24] MiRNA is the specific kind of RNA that is the

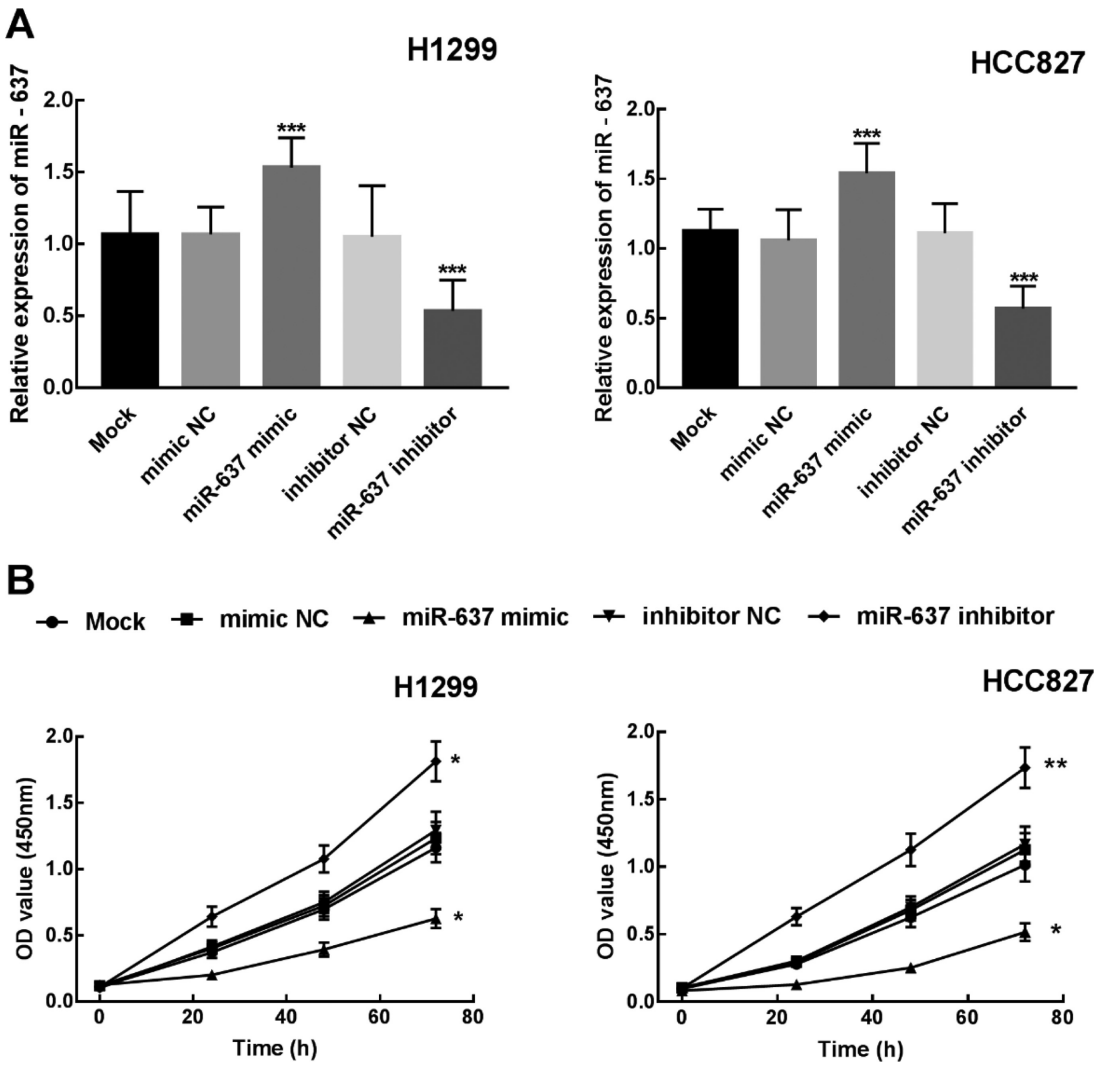

Figure 3 Inhibitory effect of miR-637 on NSCLC cell proliferation. **A.** The expression level of miR-637 in H1299 and HCC827 cells after cell transfection. ***$P < 0.001$. **B.** The proliferation of NSCLC cells with overexpression or knockdown of miR-637. *$P < 0.05$, **$P < 0.01$.

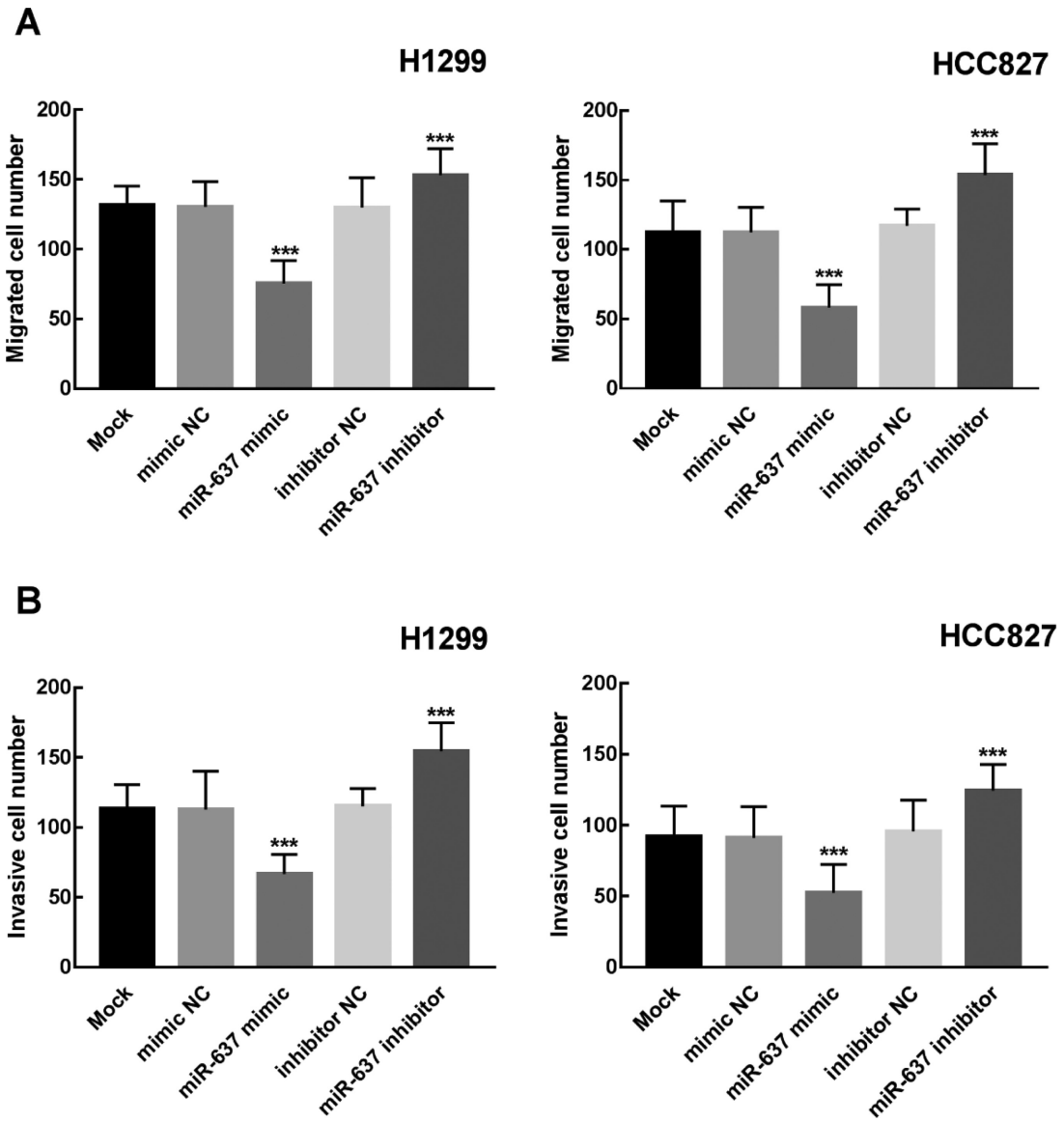

Figure 4 Inhibitory effect of miR-637 on NSCLC cell migration and invasion. **A.** The migration of H1299 and HCC827 cells with overexpression or knockdown of miR-637. ***$P < 0.001$. **B.** The invasion of H1299 and HCC827 cells with overexpression or knockdown of miR-637. ***$P < 0.001$.

focus in the study of the pathogenesis of disease at present[25]. Recent research has focused on miRNAs and other molecules as a promising approach to regulate disease progression and predicate the prognosis of various cancers.[26] In gastric cancer, miR-338−3p, a downregulated miRNA, was identified to predict an unfavorable prognosis of patients.[27] miR-340−5p was demonstrated to promote the progression of thyroid cancer by regulating the expression of BMP4, which can be a promising target for the therapy of thyroid cancer.[10]. miR-541 is a downregulated miRNA in NSCLC, which was reported to inhibit the growth and metastasis of NSCLC cells by targeting TGIF2.[28]. Moreover, the expression pattern of miRNA has some tissue specificity. For example, miR-590 was upregulated in ovarian cancer and promoted cancer progression,[29], while it was downregulated in osteosarcoma and inhibited disease progression by targeting SOX9.[30]

A number of dysregulated miRNAs in NSCLC have been identified in the previous studies. Notable findings of this study showed the decreased expression of miR-637 in NSCLC tissues and cell lines, which is consistent with the previous result of the miRNA expression profile in NSCLC.[16] Deregulation of miR-637 has recently been observed in many other human cancers. Decreased expression of miR-637 was observed in cholangcarcinoma and the overexpression of miR-637 caused a significant increase in the proliferation and migration ability of cholangcarcinoma cell QBC939.[21] Downregulation of miR-637 was reported to be associated with the TNM stage, which indicated that miR-637 might be involved in the disease progression of NSCLC.

The prognosis prediction could provide basis for adjusting therapeutic strategies. The prognostic value of miR-637 has been demonstrated in glioma that reduced expression of miR-637 was associated with the poor prognosis of patients

and identified as an unfavorable prognosis marker in glioma.[17] Here, the obtained survival information of NSCLC patients showed that downregulation of miR-637 predicates the poor prognosis of patients, which makes it act as an independent prognostic indicator for NSCLC. Previous studies have reported the potential biological function of miR-637 in various cancers. For example, miR-637 was considered as a suppressor of hepatocellular carcinoma by regulating signal transducer and activator of transcription 3 (Stat3).[18] Another study demonstrated that miR-637 could inhibit cell proliferation and induce apoptosis of human pancreatic ductal adenocarcinoma by targeting Akt1[20] Several studies have focused on the identification of prognostic biomarkers of NSCLC, but the statistical validation alone was not sufficient.[31-33] The prognosis of patients is associated with the disease development. The role of miR-637 in the development of NSCLC was further explored. The expression of miR-637 was regulated in NSCLC cells and found that miR-637 acted as an anti-tumor miRNA due to its inhibitory effect on cell proliferation, migration, and invasion of NSCLC.

The neglect of mechanical research is a limitation of this study. Previously, Akt1 has been validated as a direct target of miR-637 in its suppressed effect on cell growth, migration, and invasion of hepatocellular carcinoma and glioma.[17,34] It is speculated that Akt1 might also serve as the direct target of miR-637 in NSCLC, which needs to be verified by a deep mechanical investigation. On the other hand, *in vivo* experiments are also effective methods to assess the biological function of miR-637 in the disease progression of NSCLC *in vivo*. However, the above findings also provide a direct reference for further studies to some degree.

Based on these findings, miR-637 was identified as a significantly downregulated miRNA in NSCLC, which was associated with the TNM stage and poor prognosis of patients. Further, miR-637 was an independent prognostic indicator for NSCLC patients and acted as a suppressor in the proliferation, migration, and invasion of NSCLC cells. This study provides a novel potential biomarker and therapeutic target for the prognosis and treatment of NSCLC.

Funding

No fund.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Binzhou Medical University Hospital (NO.: 20101201).

Consent to participate

Individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Competing Interests

The authors have declared that no conflict of interest exists.

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ORIGINAL ARTICLE

A pilot study on the use of the super dimension navigation system for optimal cryobiopsy location in interstitial lung disease diagnostics

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KEYWORDS
Interstitial lung diseases;
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Super dimension

Abstract
Background: Transbronchial cryobiopsies has become increasingly important in the diagnostic workup for interstitial lung diseases. The rate of complications and mortality are low compared to surgical lung biopsies, but the diagnostic yield is not as high. The reason for the lower diagnostic yield could in some cases be explained by biopsies taken too centrally or in less affected areas. In this pilot study we examined the feasibility of using the electromagnetic navigation system, superDimension (SD), when performing cryobiopsies to increase the diagnostic yield.
Methods: Electromagnetic navigation bronchoscopy and cryobiopsies were performed using SD. An electromagnetic board placed on the back of the patient and a position sensor at the tip of the navigational probe created a real-time 3D reconstruction of previously acquired computer tomography images. The procedure was performed with the patients in general anesthesia using a rigid bronchoscope when performed in Florence and with a flexible bronchoscope through an orotracheal tube when performed in Aarhus.
Results: In total, 18 patients were included. Five patients were excluded, partly due to technical difficulties. Disposable 1.7 mm cryoprobes were used in Aarhus, and reusable 1.9 mm probes in Florence. Pneumothorax was detected in three (23%), mild hemorrhage was seen in one (8%) and moderate hemorrhage in six (46%). The biopsies contributed to the diagnosis in 11 of the patients (85%).

The authors do not have any competing interests to declare regarding this study.

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Conclusion: Using superDimension electromagnetic navigation system when performing cryobiopsies is feasible. A larger prospective trial is necessary to homogenize the technique between centres and to evaluate diagnostic advantage and complications.

Background

Transbronchial cryobiopsies (TBCB) have gained increasing interest in the diagnostic workup of interstitial lung diseases where lung tissue is needed for a confident diagnosis. Compared to surgical lung biopsies, the procedure is associated with fewer complications, morbidity and mortality. The diagnostic yield of TBCB is not as high, but still close to that of surgical lung biopsies (75-85% vs. 90-98%).[1–6]

At the moment, most centers use high resolution computed tomography (HRCT) to identify the optimal site for biopsy and fluoroscopic guidance to reach the designated biopsy site. The optimal location is app. 10 mm distance from, and with a perpendicular relation between the probe and the thoracic wall. When biopsies are taken from the lateral parts of the lower lobes, it is relatively easy to ensure correct perpendicular position of the cryoprobe by fluoroscopy. However, when the biopsies are taken from the posterior parts of the lower lobes, in the middle lobe/lingula or in the upper lobes, it is more difficult to assess if the probe is in the right position. In approximately 10-25% of all TBCB, a confident pathological pattern is not obtained.[2,5,6] The reason behind the lack of diagnostic yield is multi-factorial but a biopsy that is taken in a central part of the lung and including mainly conducting airways or in a less affected non-representative area of the lung are the main causes. There are many unexplored options combining the TBCB procedure with navigation systems. Some of these are already being used as tools together with the bronchoscope in other contexts, for example electromagnetic based navigated bronchoscopy or ultrasound guided biopsies in the diagnosis of peripheral lung lesions.[7,8] The superDimension electromagnetic navigation system is a technology that can be used together with bronchoscopy and enables real-time tracking of the navigational probe and thus provides accurate guidance to the desired area from where to perform the biopsy. It is a system developed for navigation to peripheral lesions in the lungs that are difficult to reach. For the procedure, three devices are needed; a planning software that converts the computed tomography (CT) scan into multiplanar images to reconstruct three-dimensional images of the airways; a steerable probe that contains the position sensor and an electromagnetic board connected to the computer containing the planning data.

A similar technique to guide the bronchoscopist to the optimal biopsy segment in suspected ILD patients undergoing TBCB, would be of great value, especially when the areas of interest are located in difficult to reach parts of the lungs using only fluoroscopy or when there are only subtle changes. Also, this technique could result in a higher diagnostic yield and prevent some patients from having to go through a second TBCB procedure or surgical lung biopsies.

The aim of this pilot study was to explore the feasibility and safety parameters using superDimension system when performing cryobiopsies.

Method

Patients referred for TBCB as part of an investigation for interstitial lung diseases at the Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Denmark and the Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence Italy where included in this pilot study. Eligibility criteria for TBCB have previously been described.[6] Baseline demographics regarding gender, age, smoking history, lung function parameters (forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLco)), 6-minute walk test distance and lowest saturation were recorded.

All patients had HRCT performed within four weeks before the procedure. The optimal place from where to take the biopsy was discussed at a multidisciplinary team conference with participation of radiologists and pulmonologists. Patients were eligible for inclusion if any of the biopsies were to be obtained from other areas than the lateral parts of the lower lobes. A compact disc of the scan was created for the superDimension™ navigation system (ver. 6.0 (Florence) and 7.1 (Aarhus), Medtronic Inc.).

Procedure

Before the procedure, an electromagnetic board was placed on the back of the patient. The procedure was performed with the patients in general anesthesia intubated with a rigid tracheoscope (Stortz 14) when performed at Careggi University Hospital, Florence, Italy and with a flexible bronchoscope (Olympus, Tokyo, Japan), the patient being intubated with an orotracheal tube, when performed at Aarhus University Hospital, Aarhus, Denmark. All patients were monitored with oxygen saturation, blood pressure, transcutaneous carbon dioxide partial pressure and ECG during the procedure. Cryprobes from ERBE, Tubningen, Germany, were used in both centers. Bronchoalveolar lavage was performed in all patients. Subsequently, a position sensor at the tip of the navigational probe was introduced into the airways through an Extended Working Channel (EWC). In the electromagnetic field generated, the position of the sensor was calculated in real time and merged with the previously created 3D reconstruction of the patient and the place from where to take the biopsy could be found. A Fogarty balloon was then placed at the entrance of the segmental bronchus, ready to be inflated, once the biopsy was obtained to prevent bleeding. In Florence, fluoroscopy was also used right before the biopsies were taken, to make sure the probe was in the right perpendicular position beneath pleura. The cryoprobe

was cooled with CO_2 for five to eight seconds and then retracted with the frozen lung tissue attached at the tip of the probe. Four biopsies were obtained when possible. The frozen biopsies were thawed in isotonic saline and fixed in formalin and embedded in paraffin, following standard procedure.

Hemorrhage was categorized as mild if only suction was required, as moderate if installation of saline water or extra occlusion of the Fogarty balloon were required and severe if the patient became hemodynamic or respiratory unstable, or if transfusion, surgery or intensive care was needed.

Chest x-ray was routinely performed two hours after the procedure to screen for pneumothorax.

TBCB target, lobe and/or segment, size of cryo-probe, seconds of freezing, complications, and number of biopsies were recorded. All TBCB samples were discussed in a multidisciplinary setting with radiologists, pathologists and pulmonologists.

Ethics

The Regional Ethics Committee for Clinical Trials of the Tuscany Region approved the study (Identifier: 19916_oss). Approval from The Central Denmark Region Committees on Health Research Etichs was waivered upon request.

Statistics

The results are presented as mean ± standard deviation when normally distributed or as median with interquartile ranges when not normally distributed.

Results

Eighteen patients (11 patients from Aarhus, seven patients from Florence) were recruited and five patients were excluded due to technical difficulties leaving thirteen patients for analysis (Fig. 1). All patients that were excluded had biopsies taken from other areas, but were not included in the analysis. Baseline demographics can be seen in Table 1.

In the two first patients in Aarhus, a reusable cryoprobe of 1.9 mm was used and due to the time-consuming procedure, SD was only used for the first biopsy, and subsequently conventional fluoroscopy was used. These patients were not included in the analysis. After this, a disposable cryoprobe of 1.7 mm was used. In Florence, reusable cryoprobes size 1.9 mm were used in all procedures. SD was not possible in two of the patients because of difficulties in getting into the selected segment due to severe fibrosis (one patient in Florence and one in Aarhus) and in one patient due to mismatch between the navigation system and the bronchial tree (Florence). In 12 (92%) patients, biopsies were taken from the right lung (upper lobe: three, middle lobe: three, lower lobe: six) and in one patient, the biopsies were taken from the left lower lobe. Pneumothorax was detected in three of the 13 patients (23%) of which one had a chest tube inserted that was removed the following day (Table 2). Mild or moderate hemorrhage was seen in 7 (54%). None of the patients experienced severe hemorrhage or acute exacerbations. Pleura was not present in any of the biopsies from Aarhus and in Florence, these data were missing. The biopsies

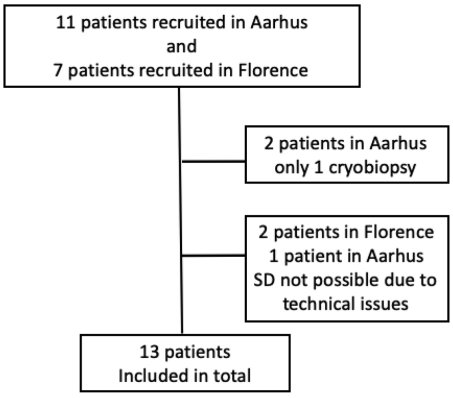

Fig. 1 Flowchart.

contributed to the diagnosis in 11 of the 13 patients (85%). The results from the two sites are presented in Table 2.

Discussion

We have in this pilot study, as the first, shown that using SD electromagnetic navigation system when performing TBCB with both rigid and flexible bronchoscopes in the diagnostic workup for interstitial lung diseases is feasible.

Performing TBCB with conventional fluoroscopy, even when guided by HRCT scans, is a blind procedure and the biopsies are not always diagnostic. Using the SD system may result in more patients having representative biopsies, a higher diagnostic yield and fewer patients being referred for new TBCB or surgical lung biopsies. In particular, in patients with only subtle changes on HRCT or in patients with changes that are more difficult to reach solely guided by fluoroscopy, the use of the SD navigation system could be beneficial, see Fig. 2. But, like all other procedures, the use of electromagnetic navigation bronchoscopy requires training, both in planning the procedure, using the software and navigating with the multiplanar CT images.

In both centers, the cryobiopsies were performed by experienced interventional pulmonologist that were already familiar with performing TBCB. In Aarhus, TR, was also familiar with using SD for retrieving tissue samples from pulmonary lesions. Even with experienced physicians, the perception was that the procedure took longer time compared to solely using conventional fluoroscopy.

In the first two patients in Aarhus, a cryoprobe of 1.9 mm was used but the procedure was time- consuming due to difficulties in navigating the cryoprobe through the EWC, and thereafter, the new disposable 1.7 mm cryoprobe was introduced for all patients.

The rate of pneumothorax was comparable to other studies using fluoroscopy guided TBCB, but the rate of hemorrhage was higher.[6,9] More Danish patients experienced moderate hemorrhage (63%) probably due to more biopsies being central compared to Florence. In Florence, fluoroscopy was used after finding the targeted area and before taking the biopsies, to make sure the probe was in the desired area beneath pleura and thus probably more peripheral. The changes found on CT in the Aarhus cohort were more pronounced more centrally which could also explain the higher rate of bleeding. Also,

Table 1 Patient demographics.

Number of patients (F/M)	Aarhus cohort8 (2/6)	Florence cohort5 (1/4)	Total cohort13 (3/10)
Age (range)	64.1 (52-80)	65.8 (57-74)	64.7 (52-80)
Ever/never smokers	6/2	4/1	10/3
FVC % predicted	94 ± 21	77 ± 26	88 ± 24
DLCO % predicted	69 ± 16	70 ± 10	69 ± 13
6MWTD, m	491 ± 115	429 ± 20	466 ± 92
6MWTD, lowest saturation, %	95 ± 3	92 ± 2	94 ± 3
HRCT pattern			
-Probable UIP	2	3	5
-Indeterminate	4	1	5
-Alternative diagnosis	2	1	3

Table 2 Procedure related data and results.

	Aarhus cohortN=8	Florence cohortN=5	Total cohortN=13
Number of biopsies per patient (IQR)	4 [4-4]	4 [4-4]	4 [4-4]
Size of cryoprobe (1.7, 1.9)	1.7	1.9	
Seconds of freezing (median and IQR)	7 [7-8]	6 [6-6]	7 [6-7]
Size of biopsies (mm and IQR**)**	5 [4.6-7.5]	6.5 [5-8]	5 [5-8]
Site of biopsies			
-Right, Upper	3	0	3
-Right, middle	1	2	3
-Right, lower	3	3	6
-Left lower	1	0	1
Pneumothorax	1 (13%)	2 (40%)	3 (23%)
Hemorrhage			
-mild	1 (13%)	0	1 (8%)
-moderate	5 (63%)	1 (20%)	6 (46%)
Contribution to diagnosis (%)	7 (88%)	4 (80%)	11 (85%)
Diagnosis			
-Hypersensitivity pneumonitis	3	0	3
-Idiopathic pulmonary fibrosis	0	2	2
-Smoking related -ILD	1	1	2
-Cryptogenic organizing pneumonia	1	0	1
-Nonspecific interstitial pneumonia	1	0	1
-Scleroderma ILD	0	1	1
-Pulmonary alveolar proteinosis	1	0	1
-Unclassifiable ILD	1	1	2

IQR: interquartile range, F: female, M: male, ILD: interstitial lung disease.

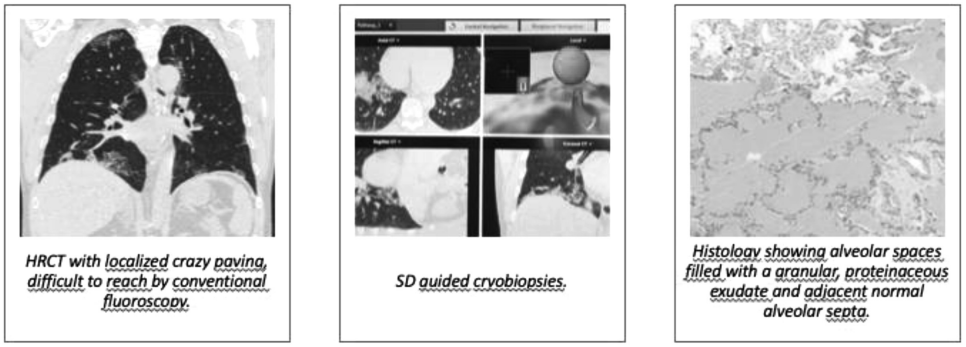

Fig. 2 SD navigation system.

pleura was not found in any of the Danish biopsies, supporting that the bleeding rate was due to biopsies being more central.[6] The perception of the degree of bleeding can be different when using a rigid bronchoscope and a flexible fiberscope. One drop of blood may block the view when working with the fiberscope while it requires more bleeding to interfere when using the rigid bronchoscope. This might influence the labeling of degree of bleeding. As in other studies with TBCB, we found a high diagnostic yield of 85%.[5,6,9]

Apart from the hardware and software for the SD, a sensor probe at the cost of approximately 1000 Euro is needed for each patient. When using conventional fluoroscopy as guidance when performing TBCB, approximately 10-25% of the biopsies are non-diagnostic. Many of these patients will have to go through a new TBCB procedure or for some, a surgical lung biopsy which will also pose a considerable cost when staff, equipment and possible hospitalization are calculated.

This study has several limitations. As this is a pilot study, the sample size is small and it is not a randomized and controlled trial comparing the diagnostic yield and risk of complications to patients having TBCB performed only with conventional fluoroscopy. Also, the study was not blinded when discussed at MDT meetings. The procedure was performed slightly different in the two centers making it more difficult to compare the results and the use of fluoroscopy might be the reason for more peripheral biopsies and less hemorrhage in the Italian patients. Based on the results in this study, we can not recommend or disadvice against the use of fluoroscopy at the same time as the electromagnetic navigation system when performing TBCB.

Conclusion

Using superDimension when performing cryobiopsies is safe and feasible. Larger randomized, controlled, single blinded multicenter trials are necessary to homogenize the technique between centres and to evaluate diagnostic yield and complications.

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The authors do not have any competing interests to declare regarding this study.

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ORIGINAL ARTICLE

Latent tuberculosis infection prevalence in second generation immigrants from high to low TB burden countries

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KEYWORDS
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Tuberculin-test;
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Nontuberculous mycobacteria

Abstract
Background: Latent tuberculosis infection (LTBI) diagnosis in a country with a low tuberculosis burden is complicated. Since the prevalence of LTBI in second generation immigrants has not been well recognized, we conducted a cross-sectional study which aimed to explore the differences in LTBI prevalence between offspring of immigrants from high tuberculosis (TB) burden countries and those whose parents were born in countries with a low TB burden.
Methods: Between May 2014 and April 2018 young native Israelis who were required to perform pre-occupational tuberculin skin tests (TST) (medical and paramedical personnel or teaching assistants of immigrants from high TB burden countries) and who had a TST result of 10 mm and above were tested for QuantiFERON-TB In Tube (QFT-GIT). Statistical comparisons were made between second generation immigrants and those with both parents from a low TB burden country.
Results: Of 102 patients, 71 were born to parents both of whom were from low-risk countries, 14 to one parent from a high-risk country and 17 to parents both of whom were from a high-risk country. The odds ratio for LTBI was 4.5 (95% CI, 1.2–17.2; p = 0.03) if both parents were born in a high-risk country compared to both parents being from a low-risk country and 4.01 (95% CI, 1.12–14.3; p = 0.03) higher compared to persons for whom at least one parent was born in a low-risk country.

Abbreviations: BCG, bacille Calmette–Guérin; CI, confidence interval; IGRA, interferon-gamma release assay; IDF, Israel Defense Forces; IMH, Israeli Ministry of Health; LTBI, Latent tuberculosis infection; Mtb, *M. tuberculosis*; OR, odds ratio; QFT-G, QuantiFERON TB Gold; QFT-GIT, QuantiFERON TB Gold In Tube; TST, tuberculin skin test; TB, tuberculosis.

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Conclusion: The risk for latent TB is significantly higher in second generation immigrants if both parents were born in a high-risk country. IGRA should be considered before treatment to patients with a positive TST if at least one parent was born in a low-risk country in order to confirm LTBI.

Introduction

Latent tuberculosis infection (LTBI) identification is a challenging task especially in countries with a low tuberculosis (TB) burden. Health care personnel undergo baseline TB screening in many countries. Guidelines recommend testing for *M. tuberculosis* (Mtb) infection by either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) for those without documented evidence of prior LTBI or TB disease.[1] Since TST is more available, easy to perform and cheaper than IGRA, it is more widely used. Although TST sensitivity is high (95%) the specificity is relatively lower (85%) than the QuantiFERON TB Gold In Tube (QFT-GIT; Cellestis Limited, Carnegie, Victoria, Australia) test (99%) due to its cross-reactivity with the bacille Calmette–Guérin (BCG) vaccination or exposure to nontuberculous mycobacteria.[2–4] Current guidelines recommend that individuals 5 years or older at low-risk for Mtb infection and disease progression in whom diagnostic testing for LTBI is warranted, should undergo a second diagnostic test if the initial test was positive.[1,5] Therefore, IGRA is frequently used to identify false-positive results of TST in order to reduce over-diagnosis and unnecessary treatment of LTBI.[6–9]

TST should be more cautiously interpreted in countries with a low incidence of tuberculosis. Immigrants from high TB burden countries make this interpretation more difficult resulting in many questions regarding TB transmission to natives or to second generation immigrants. Furthermore, the TB burden is different for each country and its transmission varies between different communities.[10] Nevertheless, transmission of TB from immigrants to native populations has been found to be low. In Norway, using molecular fingerprint patterns, little influence of M. tuberculosis transmission by immigrants from high-incidence countries to the receiving low-incidence country population was found over a period of twelve years.[11]

Treatment decisions of LTBI for immigrants from high TB burden countries is still challenging.[12–14] Long-term development of active TB appears higher in immigrants with a positive IGRA compared to TST which has reduced LTBI treatment of negative IGRA results.[15] An area of uncertainty is the prevalence of LTBI in second generation immigrants from high TB burden countries. In a study of LTBI among 9th grade school children in Norway, second generation immigrants were defined as: born in a Western country with one or both parents of non-Western origin. The risk for TST $\geq$ 15 mm was 1.53 higher than children of Western-born parents. However, the QuantiFERON TB Gold (QFT-G) test positivity risk was similar in both groups.[16]

Active TB was found to be higher among the second generation of immigrants. In one study, a higher rate of tuberculosis was seen among second generation migrants compared to native residents in Berlin.[17] In another study, TB in the second-generation was seen in 3.7–15.1% of all immigrants from high TB burden countries to the Netherlands.[18] This calls for a better understanding of TB transmission in the second generation of immigrants from countries with a high burden of tuberculosis.

Israel is a country with a very low TB burden (incidence less than 10 per 100,000 of the population)[19] and most cases of TB are in people born out of Israel according to the Israeli Ministry of Health (IMH).[20] In Israel, recent immigrants from countries with a high TB burden and persons who are pre-employment, volunteering or studying in a place with a high risk for TB infection (e.g., medical centers, nursing homes, working with immigrants from high TB countries) must undergo a TST. If the two step TST > 10 mm, the patient must be referred to a TB clinic in order to consider further testing and treatment with 4 months rifampin or 9 months isoniazide.

The aim of this study is to explore the differences of LTBI in young native Israelis (18 years old and above), among those who were born to parents from low TB burden countries and second generation immigrants from high TB burden countries. Our hypothesis is that LTBI is more prevalent in offspring of immigrants from countries with a high TB burden than others whose parents were born in countries with a low TB burden. Since at-risk pre-occupational LTBI investigation in Israel is performed by TST, we offered the QFT-GIT to individuals with a TST of 10 mm or more and considered positive QFT-GIT as an indicator for LTBI.

Methods

In this cross-sectional study we recruited civilians and soldiers who were required by the IMH to have TST (TUBERSOL, 5 TU in 0.1 ml, Medici Medical Ltd, Israel) before at-risk occupations. In Israel, soldiers who are designated to work as dental assistants or teaching assistants of immigrant children from countries with a high TB burden as well as civilians from the medical or paramedical professions are required to have TST prior to the potential exposure. In this study, healthy individuals, who had never been exposed to patients with TB, and who had a pre-occupational TST of 10 mm or above (two steps if indicated) according to their healthcare providers were offered testing by the QFT-GIT. The whole-blood assay of QFT-GIT was performed according to the manufacturer's instructions (Cellestis, Ltd., Victo-

Table 1 Participant's characteristics and results.

Risk group[a]		Total	Low	Medium	High	p-Value
No.		102	71	14	17	
Age (years)	Mean (sd)	21.1 (3.4)	21.7 (3.5)	19.9 (2.6)	19.8 (2.5)	0.005
TST (mm)	Mean (sd)	14.8 (5.0)	14.9 (5.3)	14.2 (3.9)	14.7 (4.4)	0.91
Gender (%)	Female	80 (78.4)	51 (71.8)	12 (85.7)	17 (100.0)	0.031
	Male	22	20	2	0	
IGRA (%)	Negative	89 (87.3)	65 (91.5)	12 (85.7)	12 (70.6)	0.065
	Positive	13	6	2	5	

[a] Low-both parents were born in a low TB burden country, Medium-one parent was born in a high TB burden country, High-both parents were born in a high TB burden country. TST-tuberculin skin test; IGRA- interferon-gamma release assay.

Table 2 Odds ratio for positive quantiferron test.

Risk group[a]	Odds ratio	95% CI; p-value
High risk vs. low risk	4.5	1.2–17.2; 0.03
High risk vs. medium and low risks	4.01	1.12–14.31; 0.03
High and medium risks vs. low risk	3.16	0.96–10.4; 0.057

[a] Low-both parents were born in a low TB burden country, Medium-one parent was born in a high TB burden country, High-both parents were born in a high TB burden country. CI-confidence interval.

ria, Australia) at the Laboratory of Pulmonary and Allergic Diseases,Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel. Other inclusion criteria were: signing an informed consent, age 18 years or older and native Israeli men and women. We included in the study adult children of at-least one parent that was born in a high TB burden country (incidence rate of at least 40 per 100,000)[19] as well as -those whose parents were both born in low TB burden countries. Participants were considered ''low-risk'' if both parents were born in a low-risk country for TB, ''medium-risk'' if one parent was born in a high-risk country and ''high-risk'' if both parents were born in a high-risk country.

Exclusion criteria were: prior exposure to patients with tuberculosis (active or past), working/volunteering with high-risk populations or in a medical institution, living in a high-risk country, immunocompromised patients, HIV carriers, pregnancy, acute illness or less than 4 weeks since a live vaccination such as HBV or MMR.

Study participants were asked to fill a demographic and risk-stratification questionnaire that included the country of birth of each parent, known exposure to persons with active tuberculosis, working or volunteering in a medical institute or having travelled to high risk countries for more than a month. Their BCG vaccination record and physical examination for a BCG vaccination scar were noted. The study was approved by the Institutional Review Boards of Sheba Medical Center, Tel-HaShomer, Israel and of the Israel Defense Forces (IDF) Medical Corps.

Statistical analysis

Comparison between risk groups (Table 1) was performed using ANOVA for continuous parametric variables, and the Kruskal–Wallis rank-sum test for non-parametric variables. Independence between binomial categorical variables was tested using Fisher's exact test. We looked at correlations using Pearson's test for continuous parametric variables and Spearman's rank test for non-parametric variables. Odds ratios for evaluating risk between groups were calculated using logistic regression (Table 2). Statistical analysis was performed using R software, version 3.4.1 (R Project for Statistical Computing).

Results

Between May 2014 and April 2018 one hundred and fifteen patients were recruited to the study, 8 patients had exclusion criteria, two participants did not take the QFT-GIT test and 3 blood tests results were technically disqualified. Of the 102 participants, 71 were ''low-risk'', 14 were ''medium-risk'' and 17 were ''high-risk'' (Fig. 1). Table 1 summarizes participant's characteristics and results. The mean age was 21.1 years (±3.4), and was slightly higher in the low-risk group ($p = 0.005$); this, however, is not clinically significant. There were a higher proportion of women (80.4%) and the high-risk group was exclusively females. The TST results were between the study cut-off of 10 mm and 35 mm with a mean of 14.8 (± 5) without significant differences between the groups ($p = 0.91$).

Positive IGRA risk stratification

The overall differences between the 3 risk groups were not statistically significant for a positive QFT-GIT result ($p = 0.065$). However, statistically significant differences in the prevalence of LTBI was found between the high and the low-risk groups, with an odds ratio [OR] for a positive test result of 4.5 (95% confidence interval [CI], 1.2–17.2; $p = 0.03$) for the high-risk group (Table 2). When we combined the medium and the low-risk groups, and compared them to the high-risk group, the statistically significant difference remained, with an OR for LTBI of 4.01 (95% CI, 1.12–14.3; $p = 0.03$) for the high-risk group. However, when we combined the high and medium groups and compared them to the low-risk group we found borderline significance for LTBI if at least one parent was born in a high TB burden country (OR: 3.16 (95% CI, 0.96–10.35; $p = 0.057$)). Due to the small number of positive IGRA results, comparisons according to the country of origin of the parents were not

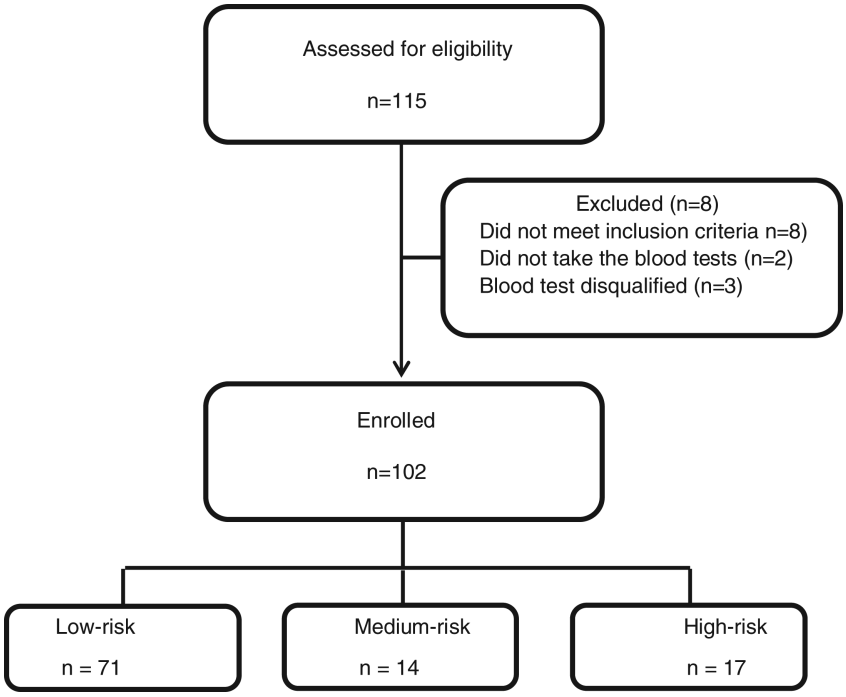

Figure 1 An overview of the study recruitment.
Low-risk: both parents were born in a low TB burden country; Medium-risk: one parent was born in a high TB burden country; High-risk: both parents were born in a high TB burden country.

justified. In the positive IGRA groups 5 participants in the high risk category were born to immigrant parents from the former USSR (2), Romania (1), Ethiopia (1) and Brazil (1). Of 8 persons in the medium risk category, one participant had a parent who had immigrated from Morocco, and another participant had a parent who had immigrated from South Africa; the other 6 participants were born to native Israelis (low risk classification).

TST and IGRA

We did not find a correlation between TST size and positive QFT-GIT results ($r = 0.18$) for the entire group. However, we found a substantial positive correlation for positive IGRA and higher TST results ($r = 0.61$, $p = 0.02$) in the medium risk group. We did not find any correlation between the positive IGRA and participants with a TST of 15 mm or greater ($r = 0.14$). Also, we did not find any correlation between age or sex and either TST size or a positive IGRA results.

BCG vaccination

Only six participants had received BCG vaccination at birth. Five were in the high-risk group, and only one of them had a positive IGRA result. One participant in the low-risk group who was born at a time when all Israeli newborns received the BCG vaccination (until 1982) had a negative IGRA result.

Discussion

LTBI rates are influenced by contact with active TB patients. Second generation immigrants from countries with a high TB burden are potentially at greater risk for LTBI than native people of the same age. However, second generation immigrants may have one immigrant parent from a high burden country or two immigrant parents from the same or different countries with high TB burdens. Furthermore, immigrant communities from different countries have different socioeconomic status which may lead to a different risk of TB transmission.[10,18,21] For example, the extent of within-country transmission is much lower (about half) for the Turkish and Indonesian communities than for the Moroccan population in the Netherlands.[18] These findings call for further contact investigation with a focus on differences between communities such as the number of residents in a house, living with grandparents or other family members, community activities, population density and other socioeconomic parameters. Other studies have shown that foreign patients in high-income countries, especially low socioeconomic groups are at high risk for disease progression.[22,23]

In this study we evaluated the prevalence of LTBI (defined by both TST of 10 mm or more and a positive IGRA result) in second generation immigrants from countries with a high TB burden. We found an OR of 4.5 (95% CI, 1.2–17.2; $p = 0.03$) for LTBI if both parents were born in a country with a high TB burden (high-risk group) compared to parents from a low TB burden country (low-risk group) that was statistically significant. The risk for LTBI remained significantly higher if we combined the medium risk group (one parent from a high TB burden country) and the low-risk group (OR, 4.01; 95%

CI, 1.12–4.31; p = 0.03). However, when we combined the medium and the high-risk groups, we found borderline significance for higher risk for LTBI if at least one parent was born in a high TB burden country compared to both parents from a low TB burden country (OR 3.16; 95% CI, 0.96–10.4; 0.057). These findings may indicate that TB transmission in a country with a low TB burden would require an extensive level of exposure to immigrants from high TB burden countries. A recent study showed that US-born individuals from neighborhoods with a high population density and neighborhoods at a socioeconomic disadvantage have a greater risk for TB transmission while race/ethnicity was a significant risk for the foreign born population.[24] Children of two immigrant parents in our study may have a higher level of exposure (parents, relatives, neighborhood and life-style) and therefore are at a greater risk for LTBI. In Berlin, second generation immigrants had a 2.2 greater risk for tuberculosis than natives, at a younger median age (27.5 vs. 52 respectively).[17] In a study among school children in Norway, although the risk for positive TST in second generation immigrants was higher (1.53) than children of Western-born parents, similar rates of positive QFT-G test were found.[16] However this study is different from our study in several aspects. First, the group of second generation immigrants was defined as one or both parents from a non-Western country. Second, the burden of TB in the country of origin was not specified and third, the study population was younger (9th grade school children). In a large study of risk factors for LTBI among recruits undergoing basic army training in the US, living with a family member who was not born in the US had an OR of 13.2, 9.3 and 6 for positive TST, QFT-GIT and T-SPOT results respectively.[5] Our results call for further studies in a larger population in order to better identify the risk of second generation immigrants from a high TB burden country.

In this study we did not find a correlation between the TST size and a positive QFT-GIT test for the entire study population. However, in the medium risk group a substantial positive correlation for positive IGRA and higher TST results was found (r = 0.61, p = 0.02). This result should be cautiously interpreted since this was the smallest group in the study (n = 13). In the study of school children in Norway, the proportion of positive QFT-G tests increased with the size of the TST indurations, however, positive tests were seen for all TST sizes.[16] In another study in children in the US, increasing TST size was associated with a trend towards increased rates of IGRA positivity, however, this was not seen uniformly even in children with very large TST indurations.[25] Several studies in the era prior to IGRA use risk assessment questionnaires for target screening for LTBI.[21,26,27] Since the induration size of the TST cannot predict positive IGRA, we believe that the risk assessment questionnaire should be updated based on larger studies using both TST and IGRA.

The major limitations of this study are the small number of participants especially of the second generation group and the higher proportion of females who were the major participants of the army occupational training courses. This may be explained by the small numbers of eligible persons for LTBI screening in Israel, and the low positive TST rate. Another obstacle for participation was the fact that IGRA blood tests were performed in many instances in a different location to that of the recruitment which reduced the number of recruited persons who were willing to travel in order to perform the blood test. The smaller number of second generation immigrants precluded a risk stratification analysis of the country of origin and other demographic factors such as years since parent's immigrations, living with grandparents, parents' divorce and travelling to high-risk countries. A general limitation of LTBI studies are the lack of a gold-standard test for *M. tuberculosis* infection. However the dual TST and IGRA test reduces the false-positive results.

LTBI in second generation immigrants has not yet been well studied. In our small study we found that second generation immigrants in a low TB burden country are at a significantly higher risk for LTBI only if both parents were born in a high-risk country. However, larger studies should be conducted in order to better understand TB transmission in this group and special recommendations for screening should be put in place. Since in a low TB burden country the risk of LTBI for non-immigrants is very low, an IGRA should be considered before treatment of patients with a positive TST if at least one parent was born in a low-risk country.

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CRedit authorship contribution statement

D. Shlomi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing. **I. Galor:** Methodology and Supervision. **A. More:** Data curation and Project administration. **B. Oberman:** Formal analysis and Writing - review & editing. **L. Fireman:** Formal analysis, Investigation and Resources.

Ethics committee approval

The study was approved by the Institutional Review Boards of Sheba Medical Center, Tel-HaShomer, Israel and of the Israel Defense Forces (IDF) Medical Corps.

Clinical trials no. NCT02073669.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Inhaler technique knowledge and skills before and after an educational program in obstructive respiratory disease patients: A real-life pilot study

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KEYWORDS
Education;
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Abstract
Introduction and objective: Patients present poor knowledge and skills about their respiratory disease and inhaler device. We aimed to: (1) evaluate COPD and asthmatic patients' ability to manage inhaled drugs (2) identify differences among devices and (3) correlate clinical data with patient ability.
Material and methods: Patients ($n = 134$) admitted for pulmonary rehabilitation (PR) were given an ad-hoc questionnaire covering 0% as the worst and 100% the best value of global ability (indicating the sum of knowledge and skills in managing inhaled drugs) at baseline (T0) and discharge (T1). Educational program was provided during PR. Setting of rehabilitation, age, sex, diagnosis, spirometry, CIRS score, level of autonomy to use medications, if naïve about PR, educational level, and number/type of prescribed inhaled drugs were recorded.
Results: Most patients used 1 drug while 37% used 2 drugs. DPIs were the main device prescribed. At baseline, patients' mean level of knowledge and skills were 73% and 58%, respectively. There was a significant difference in level of skills ($p = 0.046$) among device families, DPIs resulting worst and pMDIs best. Global ability, skills and knowledge improved after educational support ($p < 0.001$) but did not reach the optimal level, 88%, 87% and 89%, respectively. Baseline global ability was positively correlated to female gender, younger age, previous PR access, outpatient status, higher education level and GOLD D class.
Conclusions: At hospital admission, global ability was not optimal. Education may improve this, irrespective of the type of device used, in particular in male, elderly, naïve to PR, low educational level patients.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory pulmonary diseases affecting millions of people worldwide.[1] Inhaled therapy can be delivered via nebulizers, pressurized metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs). Studies consistently report that many patients with asthma and COPD do not use their inhaler devices correctly.[2,3] Indeed, medications cannot be effective if they do not reach the sites they are intended to target.[4,5] Poor inhaler technique stems from the fact that patients often poorly understand the purpose of and how to use their inhalation device.[6] Poor adherence is common, with 50% or more of patients with asthma and COPD not taking their inhaled therapy as prescribed or instructed.[7,8] Non adherence can further perpetuate poor technique and can lead to costly exacerbations and worsening disease.[7,8] A comprehensive patient education, including device training, can improve outcomes.[9,10] However, even with training, not all patients are able to use their inhalers correctly.[11]

The aims of this study were: (1) to evaluate with a simple interview the global ability, knowledge and skills in managing inhaled drugs before and after an educational program during rehabilitation for obstructive respiratory disease patients; (2) to compare, if any, differences among the prescribed devices; and (3) to correlate clinical and anthropometric data with the overall ability to manage drugs.

Methods

This observational qualitative study considered a cohort of patients attending the Respiratory Unit of the Istituti Clinici Scientifici (ICS) Maugeri of Lumezzane (Bs), Italy. The study was conducted in a single center and approved by ICS Maugeri IRCCS Ethics Committe (EC 2322; 16 July 2019). All participants were informed and gave their written consent to participation.

Patients

Consecutive patients aged >18 years with a diagnosis of COPD or severe asthma were eligible for enrolment. COPD and asthma were defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[12] and Global Initiative for Asthma (GINA) guidelines.[13] Patients were admitted either to an inpatient program with an average stay of 25 (SD 3) days or an outpatient program attending no less than 22 rehabilitative sessions with 2 or 3 weekly accesses over a 2-month period. Indication and prescription for pulmonary rehabilitation (PR) was not based only on FEV_1 value, but according to a previously published internal triage,[14,15] generating a Pulmonary Rehabilitation Decisional score (PRDS). PRDS considers several items such as lung function, clinical parameters, disability, frailty, and participation in ADLs and has been used for staging the clinical priority of PR prescription and choosing the PR setting (inpatient or outpatient). Anyway, all patients coming from acute hospitals have been inserted in the ''inpatient group''. Patients were followed by a pulmonologist and nurse case managers, nurses, respiratory therapists and others pulmonologists. The proposed PR programs were based on classical guidelines indications[16] based on aerobic training, calisthenics, lower and/or upper limb selective muscle strengthening, balance training, inspiratory muscle training and secretion assistance when indicated. During the PR program drugs adjustments (in terms of quality and quantity) were carried out according to guidelines and clinical needs.

Exclusion criteria were: dyspnea at rest with need for acute hospitalization, oncological disease, terminal illness, neuromuscular degenerative diseases, severe orthopedic diseases, subject bedridden or confined to a wheelchair, and altered cognitive status measured by MMSE[17] < 22.

Intervention

Development of the interview

To obtain a questionnaire with face validity based on expert opinion involving a structured process of consensus, we engaged key stakeholders (4 doctors and 4 nurses) from among health staff employed in the rehabilitation field of our Institute. We performed a systematic review of the COPD literature identifying items to use for the questionnaire and prepared a preliminary draft of questions. During the meeting, using a Delphi-like procedure, we asked the experts to rate the accordance of preselected items on a 5-point Likert scale (0 = totally disagree; 1 = disagree; 2 = sufficiently agree; 3 = moderately agree; 4 = totally agree). Consensus was considered when more than 75% of the respondents rated each item as totally agree. Finally, the focus group checked that the wording of each question was simple, clear, and comprehensible (details in supplementary material).

The final tool consisted of 8 questions enquiring about: the name of the drug/drugs, dosage prescribed, time of administration during the day, ability to distinguish the drug/s from others, the usefulness, and how to prepare, use and replace the drugs (Fig. 1). The operator scored each item dichotomously, according to the patient's response, as knows/does not know or correct maneuver/incorrect maneuver (Fig. 1). The score for part A (representing the percentage of correct answers for knowledge) and that for part B (representing the percentage of correct maneuvers for skills) were added up to give a final total global ability score (A + B), 0% was the worst and 100% the best value of global ability (details in supplementary material).

Interview

Before conducting the interviews, all nurse staff participated in a briefing session on how to conduct the interview in a standardized way. According to the previous literature[18] a list of possible mistakes/error for incorrect drug use was prepared. Nursing staff used the list during his/her interview (details in supplementary material).

The score was calculated (T0) during a face to face visit and assigned to a nurse case-manager not involved in the educational program. Patients admitted for a PR program, either as inpatients or outpatients, underwent the

Patient Interview Chart

TEST: ▫ INITIAL ☐ DISCHARGE

NAME……

AGE …… EDUCATIONAL LEVEL…….. SETTING……..

Independent in drug preparation/administration ▫

Dependent in drug preparation/administration ▫

Number of drugs: …….

DRUG PRESCRIPTION BY DOCTOR				
DRUG NAME		ASSOCIATED DEVICE (MDI, DPI, SMI)	DOSAGE	SCHEDULED
PATIENT INTERVIEW				
			Correct answer	*Wrong answer*
	Part A (Knowledge)			
1	Tell me the name of the drug used for your lungs			
2	How many times a day do you take this drug?			
3	At what time of the day do you take this drug?			
4	Show me, among all these drugs, the one/s you are taking			
5	Can you tell me what the drug is for?			
	SUM OF ANSWERS (0-5)			
	% CORRECT ANSWERS			
	Part B (Skills)			
1	Can you show me how you prepare the drug?			
2	Can you show me how you take your drug?			
3	What do you do at the end of the inhalation of the drug?			
	SUM OF ANSWERS (0-3)			
	% CORRECT ANSWERS			
	Total (A+B) sum of responses (0-8)			
	% CORRECT ANSWERS			

Nurse signature _____ Date_____

Figure 1 Patients Interview Chart.

interview at the time of admission or at their first/second access.

Education program

After assigning the score and starting from the baseline level of knowledge and skills, 2 structured tailored educational meetings of 20 min each (including reminders, motivation, reinforcement, demonstration, sheets and videos material) were given by a dedicated team of 4 nurses (2 for outpatients and 2 for inpatients), different from the case manager, to reinforce the knowledge and the correct use of the inhalation therapy, in such a way as to be able to intervene promptly and effectively if the therapy was not performed correctly (details in supplementary material).

The form for verification of change in knowledge and skills to inhalation therapy was re-administered to the patient on discharge (T1) by the same case-manager.

Measurements

The following data were collected: setting of rehabilitation, demographic data such as age, sex, definitive diagnosis of COPD based on spirometry, presence of comorbidities with the Cumulative Illness Rating Scale (CIRS),[19] present/past data on FEV_1 (% pred.) and forced vital capacity [FVC (% pred.)], if naïve to PR, educational level (no education or elementary school vs. higher than elementary school), number and type of inhaled drugs routinely used, if the patient was generally autonomous in the use of drugs. Patients were

defined as autonomous if they had an acceptable level of cognitive status and absence of dysphagia.

Statistical analysis

Statistical analysis was performed using STATA 11 (StataCorp LLC, Texas 77845-4512 USA). Continuous variables were expressed as mean ± standard deviation (SD). Binary and categorical outcomes were described as frequency and percentage in each group. A two-sample t-test comparing differences at baseline between groups and changes after education training was performed. To identify correlations between baseline characteristics and the risk of presenting a low baseline global ability (defining by value below the median of global baseline data), we performed a post hoc analysis to estimate the Odds Ratio (OR). A p value <0.05 was considered as statistically significant.

Results

One hundred and thirty-four patients were consecutively enrolled in the study. The time spent on the patient interview was 3.06 ± 1.70 min (range 1.51–6.55).

Table 1 shows baseline data of the patients. The majority of patients routinely used only one inhaled drug while 37% used 2 drugs (the majority of these had COPD). Almost all patients were autonomous regarding general use of their medication. No differences were found in device categories between COPD and asthma. The majority of patients used a DPI: Diskus (9%), Ellipta (19.8%), Genuair (23%), Nexthaler (5.7%), Turbuhaler (5.1%), HandiHaler (7.4%), Breezhaler (30.6%). Younger patients used MDIs more frequently while patients with lower FEV_1% pred. more frequently used MDIs and SMIs. When compared to the whole group, SMI group (9.7%) included patients admitted in the 60% of the cases as inpatients, older (72 ± 9 years), in 38% of cases with CRF and with higher cultural level (70% of cases). At discharge after PR, drug prescription was changed in 30% of COPD and 51% asthmatic patients, respectively (in all cases number and dosage of drugs were increased).

Patients with low education level more frequently used MDIs. No differences in the devices used at admission were found concerning comorbidities and previous PR access.

All patients attended 2 educational sessions, 37.3% of COPD patients and 18.5% of asthmatic patients needed 3 educational sessions, because the dedicated nurses found these patients were still insecure and not yet ready to perform the final interview. Patients needing more than 2 sessions were older, with lower educational level, with lower MMSE and more naïve to PR.

On hospital admission, knowledge, skills and global ability regarding inhaled drugs were not optimal with 69%, 74% and 83% of patients with level <100%, respectively. Mean and median global ability in percentage at baseline were 67.27 ± 26.26 and 68.75 (IQR 50.0–87.5), and at discharge 88.06 ± 18.82 and 100 (IQR 83.3–100) ($p < 0.001$), with mean delta improvement 20.79 ± 18.50. Fig. 2 (panel a) shows baseline (T0) and delta improvement at discharge (T1) in percentage of the global ability score and according to the components of skills and knowledge. The pre-to-post changes were all statistically significant ($p < 0.001$)

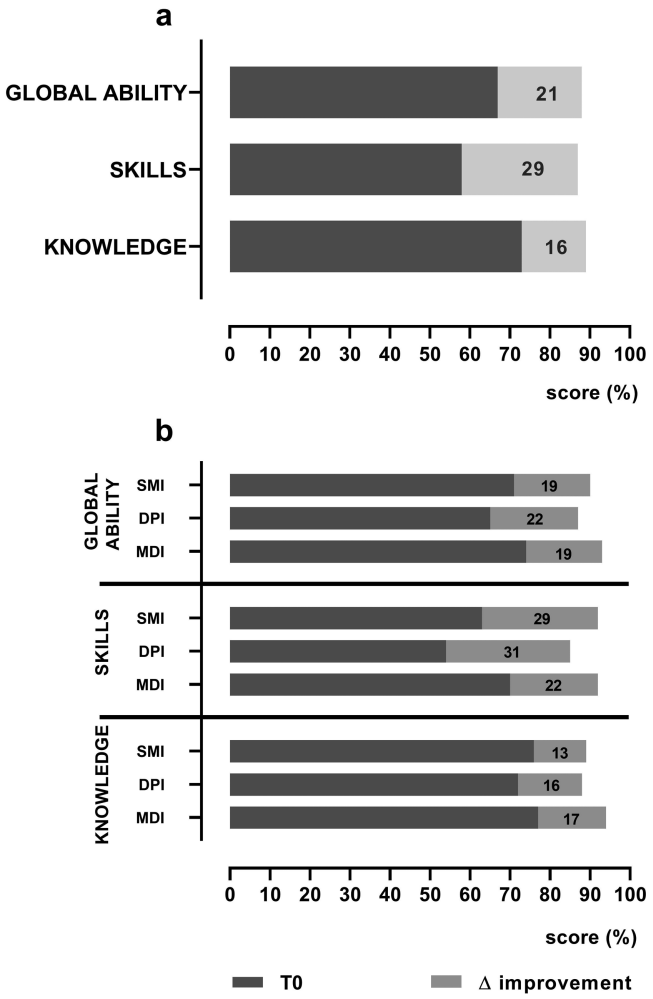

Figure 2 (panel a) shows baseline mean T0 score (dark bars) and mean delta score improvement at discharge (gray bars) in patient's global ability and the components of skills and knowledge. The pre-to-post changes (delta score improvement) were all statistically significant (p = <0.001); (panel b) shows baseline mean T0 scores (dark bars) and mean delta score improvement at discharge (gray bars) in global ability, in skills and knowledge according to different families of devices used. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler.

(panel a), the mean improvement in skills was 29.19 ± 29.61 and in knowledge 15.60 ± 20.17. In detail, 100 patients (75%) improved global ability, while 34 (25%) worsened or remained unchanged. As to skills ability, at discharge, 30% of patients were still unable to use their devices correctly.

Fig. 2 (panel b) shows baseline values and delta improvement at discharge in global ability, skills and knowledge according to the 3 different families of devices tested (SMI, DPI and MDI). Differences in the patients' global ability at baseline were not significant among the devices tested ($p = 0.144$). At baseline only, there was a significant difference ($p = 0.046$) in the patients' level of skills in using different families of devices: the DPI family being the worst and the MDI the best; the delta skills improvement after education was otherwise not different ($p = 0.262$). Patients' knowledge of devices at baseline and delta knowledge improvement after education were not significantly dif-

Table 1 Baseline characteristics of patients.

	ALL	COPD	Asthma	*p*
Patients, n	134	107	27	
Inpatient/outpatient, n	49/85	42/65	7/20	0.199
Age, years	70.34 (8.26)	70.18 (8.53)	71 (7.20)	0.646
Gender (M/F), n	92/42	75/32	17/10	0.475
FEV_1% pred.	61.47 (25.27)	55.12 (23.01)	86.63 (16.90)	**<0.001**
FVC % pred.	84.51 (23.14)	82.05 (23.14)	94.30 (20.74)	**0.013**
FEV_1/FVC	59.22 (19.52)	52.63 (14.74)	85.37 (13.19)	**<0.001**
GOLD A, %		9.3		
GOLD B, %		38.3		
GOLD C, %		8.4		
GOLD D, %		43.9		
GINA I, %			7.4	
GINA II, %			14.8	
GINA III, %			48.1	
GINA IV, %			22.2	
GINA V, %			7.5	
Educational level (elementary), n (%)	71 (53)	52 (49)	19 (70)	0.103
CIRS1, score	1.70 (0.36)	1.70 (0.37)	1.69 (0.36)	0.897
MMSE, score	25.29 (1.24)	25.02 (1.37)	26.33 (1.01)	0.631
Naive to pulmonary rehabilitation, n (%)	48 (36)	35 (33)	13 (48)	0.135
Respiratory drugs routinaly used	1.40 (0.52)	1.48 (0.54)	1.11 (0.32)	**0.001**
One, *n* (%)	82 (61)	58 (54)	24 (89)	**0.004**
Two, *n* (%)	50 (37)	47 (44)	3 (11)	**0.004**
Three, *n* (%)	2 (2)	2 (2)	0 (0)	**0.004**
Autonomy in drug use, n (%)	128 (96)	105 (98)	23 (85)	**0.004**
MDI, %	20.15	19.63	22.22	0.764
DPI, %	70.15	72.90	59.26	0.166
SMI, %	9.70	18.52	7.48	0.083

FEV_1 = forced expiratory volume at first second; FVC = forced volume capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GINA = Global Initiative for Asthma; CIRS = Cumulative Illness Rating Scale; MMSE = mini-mental state examination; MDI = metered dose inhaler; DPI = dry powder; SMI = soft mist inhaler. Where undefined, number in parentheses refers to (SD).

ferent ($p = 0.516$ and $p = 0.745$, respectively). At discharge global ability, skills and knowledge did not reach the optimal level being 88%, 87% and 89% respectively.

Table 2 shows the Odds Ratios risk to predict a low baseline global ability to use inhaler devices (less than the median value of 68.75). While female gender, younger age, previous PR access, outpatient status, higher education level and being into GOLD D class showed a protective effect on low baseline global ability to use inhaler devices, diagnosis, prior clinical classification of autonomy, $FEV_1\% < 30$, CIRS > 1.6, type of device, and use of more than one inhaled drug did not influence baseline global ability.

Discussion

This study has demonstrated that at hospital admission knowledge and skills regarding inhaled drugs were not optimal (69% and 74% of patients with level <100%, respectively). A simple, clear and short interview at admission and discharge may be a good tool to monitor patients' knowledge and skills. A tailored educational program may strongly improve this gap, irrespective of the type of device used. Based on our findings, drugs education should be targeted particularly at patients who are male, elderly, naïve to PR, with a low educational level.

Obstructive respiratory disease patients are poorly adherent to inhaler therapy. Low adherence was associated with age, current smoking status, number of respiratory drugs prescribed and poorer quality of life,[20] patients' perception of their health and medication effectiveness, and the presence of depressed mood and comorbidities.[21]

Eighty-two percent of COPD patients claimed to understand their disease and treatment, needed continuous education regarding inhalation devices.[22] The Chronic Obstructive Pulmonary Disease knowledge Questionnaire (COPD-Q)[23] explores risk of infections, use of oxygen, utility of drugs, prevention, correct time to use long-acting drugs, symptoms, smoking cessation, SABA use, and disease time course. In our study, we proposed a short simple interview oriented exclusively on drugs knowledge and skills. The rationale of the questionnaire is to focus deeply on whether patients are able to remember the name, dosage, time of use, utility and can recognize their device amongst several other devices and perform correctly the preparation, use and post-use recommendations.

Table 2 Odds ratio (OR) to predict a low baseline global ability (less than the median value of 68.75).

	OR	Standard error	*p*	95% CI
Male	2.38	0.92	0.034	1.111–5.098
Age > 65 years	2.35	0.954	0.037	1.064–5.212
Not naïve to PR	0.11	0.04	<0.001	0.049–0.262
Outpatient	0.14	0.06	<0.001	0.064–0.335
Higher educational level	0.24	0.89	0.026	0.118–0.501
GOLD D class	0.33	0.13	0.004	0.156–0.708

PR = pulmonary rehabilitation, CI = confidence interval.

In outpatient settings mistakes using inhaler devices has been found in a range of 6–71%, with 40% of patients presenting at least one vital mistake.[24–28] Muller et al.[29] found that 51.8% of patients present at least one mistake about using their devices. Molimard et al.,[8] in a large cohort of patients outside of hospital, assessed inhaler device handling and its association with exacerbations. Handling errors were found in over 50% and exacerbations were less frequent in the absence of errors, while they doubled in the presence of critical error. Melani et al.[30] in a large cohort of both asthmatic and COPD patients found that critical mistakes were no fewer in DPIs than in MDIs: in 12% for MDIs vs. 35% for Diskus and HandiHaler, and 44% for Turuhaler. In patients referred for a chest visit, inhaler-specific errors were as follows: Aerolizer 9.1%, Diskus 26.7%, HandiHaler 53.1% and Turbuhaler 34.9%.[31]

Only one study was conducted in an inpatient setting—it found that misuse was common in COPD (86% with MDI and 71% with Diskus).[32] The lower level of misuse and errors found in our sample (60% for drugs skills) may be due to the particular rehabilitative setting, i.e. 64% of patients were not naïve to PR, probably already confident with regard to drug education, with mixed diseases (asthma and COPD) and attending PR as both out- and inpatients. DPIs derive the energy for the emptying of the drug system from the user inspiratory flow: the failure to achieve a forceful inspiratory flow through a device was the most common critical mishandling error with DPIs in Melani et al.'s study.[30] In fact, in our study, COPD patients with a DPI were less able than patients with an MDI or SMI to use their devices, probably due to their severe functional limitation.

Critical errors and inability to improve after an education program found the following factors: older age,[30,31,33] lower schooling[30,33] and lack of instruction received,[30,31,33–35] cognitive impairment or dyspraxia,[36] use of 2 or more inhalers,[34,36] and severity of airway obstruction.[31] Our study confirms that age, lack of a previous educational program, and low level of education are negative predictors for drugs use ability; as a novel finding, we also demonstrated that female gender and outpatient regime (as opposed to inpatient) are protective factors. It is noteworthy that female patients seem to do better: possible explanations are that this group presented a higher cultural level (in 57% of cases) and fewer naïve to PR (14%) when compared to males (43% and 40%, respectively). At the same time, it is not unexpected that outpatients group was better than inpatients due to a lower age (70 ± 8 years old), a better level of airway obstruction (67 ± 24% pred), more frequently with asthma (23%) and with a very low number of patients unable to use drugs (2.3%). Finally, it is interesting that only the more severe patients belonging GOLD D class presented a lower risk of having global inability: the possible explanation is that this group had attended previous PR program and education in the 76% of cases and, being more symptomatic, used more drugs with a higher adherence.

The lack of education by health caregivers on inhaler technique significantly increases the risk of misuse for all the studied devices.[30,37] One study assessed errors with different devices in asthmatic and COPD patients after they had read the patient information leaflet:[24] fewer COPD patients made critical errors with Ellipta (5%) than with other devices, and most patients (57–70%) did not require health-operator instructions using Ellipta, but instructions were required for Diskus (65%), MDI (85%), Turbuhaler (71%), HandiHaler (62%) and Breezhaler (56%).

Different training programs of diverse intensity and content (individual interviews about beliefs and behavior related to adherence, information about the illness and training about inhalation techniques, video) have been proposed, with patient skills' improvement ranging from 20 to 79%.[26,35,38–40] In our sample, the mean improvement in skills was 29.19% while that in knowledge was 15.60%: these delta differences are clearly related to lower baseline values allowing more space for improvement (Fig. 2).

Limitations and strengths

Limitations of the study are the small sample size, the subjective basis of our findings (based on researcher-s judgment), the lack of a comparison control group and the fact that knowledge and skills measurement were not related to clinical outcomes. Another limitation is the use of a questionnaire with a dichotomous yes/no answer where the different skill capacity steps depended on a single answer grouped together. Strengths of our study are: (1) the simplicity of a questionnaire exclusively dedicated to drugs knowledge and skills; (2) the relatively short time needed to administer it, favoring its potential for routine use; (3) the comparison among different devices available in the market and (4) the presented data on a selected population admitted to a rehabilitative center.

Conclusions

The findings were predominantly confirmatory of previous literature covering patients' lack of skills and knowledge about inhaled drugs, anthropometric, clinical and functional

features which influence patients' global ability. The study adds that an educational program may improve this gap, irrespective of the type of device used, in patients who are male, elderly, naïve to PR, with a low educational level.

Author contributions

MV, MF, EM, LC designed the study and draft the manuscript.

MF, EM, LC performed educational assessment and reviewed the manuscript.

MP and LB performed statistical analysis and reviewed the manuscript.

GB, CZ, AP, DF performed clinical assessment and reviewed the manuscript.

All the Authors approved the definitive version of the manuscript and declare that questions related to the accuracy or integrity of any part of it have been appropriately investigated and resolved.

Conflict of interest

MV declares conflict for consultancy for or receipt of speaker's fees from Boeheringer; all the other Authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2020.04.010.

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ORIGINAL ARTICLE

Diagnostic and therapeutic approach of central sleep apnea in heart failure — the role of adaptive servo-ventilation. A statement of the Portuguese society of pulmonology and the Portuguese sleep association

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Abstract It is known that patients with heart failure (HF) have an increased risk of developing central sleep apnoea (CSA), with Cheyne-Stokes respiration. The development of servo-ventilation aimed to treat CSA and improve the quality of life (QoL) of these patients. A large randomized clinical study, SERVE-HF, was conducted in order to test this theory in patients with HF and reduced ejection fraction (HFrEF). The results from this trial seemed to indicate that, in these patients, there was no beneficial effect of the assisted ventilation in CSA treatment. More surprisingly, an increased rate of all-cause or cardiovascular mortality was observed. This has led to dramatic changes in clinical practice, with decreased frequency of servo-ventilation prescription across Europe, including Portugal, due to changes in the guidelines. However, SERVE-HF was conducted only in severe systolic HF patients with CSA, and caution must be taken when extrapolating these results to HF patients with preserved ejection fraction or CSA patients without HF.

The study also showed poor adherence, methodological and statistical gaps, including study design, patient selection, data collection and analysis, treatment adherence, and group crossovers, which have not been discussed in the trial as potential confounding factors and raise several concerns. Moreover, the adaptive servo-ventilation (ASV) device used in SERVE-HF was unable to lower the minimum support pressure below 3 mm H_20, and this has been suggested as

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one of the probable contributing reasons to the excess mortality observed in this study. This limitation has since been solved, and this ASV device is no longer used.

This paper describes the results of a Portuguese Task Force on the treatment of central sleep apnoea in patients with chronic HF.

Introduction

Central sleep apnoea (CSA) is a co-morbidity of chronic heart failure (CHF).[1] Servo-ventilation (SV) is a method of ventilatory support designed for Cheyne-Stokes respiration (CSR) in heart failure (HF).[2]

The effects of servo-ventilation in patients with HF with reduced ejection fraction (HFrEF) and CSA were investigated in a large randomised trial — SERVE-HF.[3] Although analysis of the pre-determined primary endpoints — time to first event of death from any cause, life-saving cardiovascular intervention, or unplanned hospital admission due to worsening of HF — was neutral, results showed increased all-cause and cardiovascular mortality.[3] These results cannot be extrapolated to HFrEF with other forms of sleep-disordered breathing such as Obstructive Sleep Apnoea (OSA).[3,4]

The SERVE-HF trial showed poor adherence, methodological and statistical evidence gaps, and further research was needed to better understand its definitions, screening methods and whether and how to treat sleep-disordered breathing (SDB) in patients with HF.[5-8] A very interesting commentary explored the methodological issues of the SERVE-HF trial, including study design, patient selection, data collection and analysis, treatment adherence and group crossovers, which have not been discussed in the trial, as potential confounding factors, and raised several concerns.[9] Results from a multistate modelling analysis showed that SV was associated with an increased risk of cardiovascular death in patients with HF and Left Ventricular Ejection Fraction (LVEF) $\leq$ 45% treated for predominant CSA. This risk of cardiovascular death was found to be increased in patients not previously admitted to the Hospital, presumably cases of sudden death, and markedly increased in patients with LVEF$<$30%.[10] However, results from two real world studies showed that most patients treated with SV do not fall into the group of patients at risk, in whom SV is contraindicated.[11,12] Moreover, it has been recently shown that the increased cardiovascular mortality reported in the SERVE-HF trial may not be related to worsening of HF.[13]

A Task Force of the European Respiratory Society (ERS) addressing existing diagnostic and therapeutic standards describes the current practice of CSA treatment in HF.[14] Some of the statements were supported by a previous study, which compared the effect of SV with nasal oxygen and CPAP during polysomnography. Results showed large increases in slow-wave and rapid eye movement (REM) sleep with SV but not with oxygen or CPAP.[2] In patients with heart disease and preserved left ventricular ejection fraction (pEF), whose treatment of CSA was ASV, a significant reduction of the apnoea-hypopnea index (AHI) was observed. Based on the information available at the time, members of the ERS task force stopped prescribing SV to treat CSA in patients with HFrEF with LVEF$\leq$45% until the publication of results from new studies.[14]

Novel clinical studies to better understand the real implications of the SERVE-HF trial have been completed or are currently ongoing.

The CAT-HF trial aimed to investigate whether minute ventilation (MV) ASV improved cardiovascular outcomes in hospitalized HF patients with moderate-to-severe sleep apnoea. In these patients, adding SV to optimized medical therapy (OMT) did not improve 6-month cardiovascular outcomes. Detection of the safety signals and identification of the differential SV effects in HF patients with pEF were limitations of this study, which was terminated in 2015.[15] Nevertheless, it allowed to conclude that significant reverse left ventricular (LV) remodelling was observed among HFrEF patients with SDB, regardless of treatment allocation. Substantial reductions in left atrial volume among HFrEF and HFpEF patients receiving SV suggests that SV treatment may also improve diastolic function and warrant further investigation.[16] A proof-of-concept study showed that treatment of sleep apnoea with SV leads to reduction in atrial fibrillation burden compared with OMT alone, without an increase in ventricular tachycardia/ventricular fibrillation (VT/VF) events. However, this hypothesis should be tested in larger trials.[17]

The ADVENT-HF (NCT01128816) is an open-label multicentre, randomized study, with blinded assessment of endpoints of standard medical therapy for HFrEF alone *versus* HFrEF, with the addition of SV in patients with HFrEF and SDB, in both non-sleepy OSA and CSA. Patients with LVEF$\leq$45% are eligible for inclusion.[18] The trial is currently under recruitment (the last recruited patient is expected for 2021).

It is the authors' opinion that the SERVE-HF study was flawed due to the inclusion of HF patients that were too severe, which biased the results since only a small percentage of HF patients fall within this severity group.[11,12] The ADVENT-HF is including patients more similar to the ones found in real clinical practice, with less severe HF, and the results, when available, will be of great relevance.[7] This paper describes the main conclusions of a Portuguese Task Force for the use of SV in HF patients following the modification of guidelines due to the results of the SERVE-HF trial in 2015.

Methods

A Portuguese Task Force of nine Pulmonologists and Cardiologists, specialized in servo-ventilation in heart failure patients, convened twice to discuss the role of adaptive servo-ventilation as a therapeutic approach of central sleep

apnea in heart failure. Based on current clinical guidelines and on relevant scientific papers in the field, the conclusions of this Task Force were agreed upon in 2021.

Problems regarding the prescription of ASV

Currently there are two main problems regarding the prescription of ASV, both directly associated with the results from SERVE-HF: 1) physicians are afraid of prescribing it due to safety issues and 2) after the release of the SERVE-HF trial, in 2015, the Portuguese National Health Authority immediately issued a document recommending withdrawal of SV from patients with the same characteristics as the SERVE-HF population and not prescribing it to new patients.[19] These two reasons explain why, although prescription levels of SV have been slowly increasing in recent years, they are far from achieving the prescribing levels before 2015.

Since there are different kinds of SV, being able to analyse the Cheyne-Stokes curve and identify in advance the most suitable type of SV for each patient is crucial, and one of the issues in this identification is the value of the minimum support pressure of the devices. When patients hyperventilate, CO_2 levels decrease, which leads to a compensatory decrease in HCO_3^- to maintain the pH. This alkalosis is associated with hypokalaemia, which may lead to arrhythmia and even cardiac arrest.[7] Therefore, when the patient is in a hyperventilation phase, the support pressure should be zero because any pressure above zero will worsen the already existing hypocapnia, with the consequent cardiac alterations. On the other hand, when the patient is in apnoea, the maximum programmed pressure should be used. In fact, the ASV device used in SERVE-HF was unable to lower the minimum support pressure below 3 mm H_2O, and this has been suggested as one of the reasons that may have contributed to the excess mortality observed in this study.[7,9] This problem has since been solved, and this previous-generation ASV device is no longer used.[9]

How to overcome the results of the SERVE-HF trial?

There is currently a generalized fear of prescribing SV in patients with HFrEF$\leq$45%. Prescription of SV in patients with HFrEF$<$30% is not an issue since existing data clearly indicates that ASV is contraindicated in this group.[10,12] However, the question remains regarding EF values between 30–45%. The fact is that patients were doing well before the results of the SERVE-HF trial and SV is considered to be, overall, a very good treatment, better than CPAP[20-22] and with a better adherence to therapy.[23] Indeed, a meta-analysis from

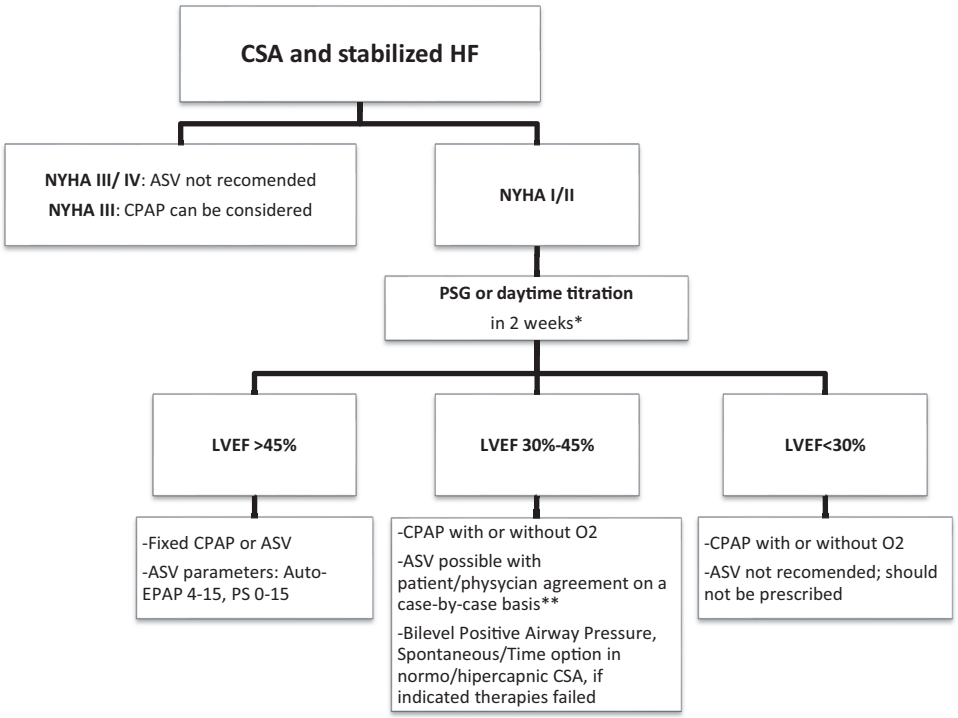

Fig. 1 Treatment of central sleep apnea in heart failure.

2012 that included studies of stable HF patients with LVEF between 20% and 55% concluded that SV was more effective than control conditions in reducing SDB severity and improving cardiac function and exercise capacity in patients with SDB and HF.[24]

An overall prescription improvement can be observed, but there are still patients who could benefit from SV and are being refused treatment. One of the main reasons is the lack of clarity in the treatment algorithm definition. This might be related to the insufficient level of resources available, which hampers diagnosis and consequently SV treatment.

Proposed algorithm

In an attempt to obtain a diagnostic and therapeutic approach for the treatment of CSA in patients with HF, the authors firstly agreed that each patient constitutes a specific case and must always be evaluated individually. In fact, the latest guidelines on SV state that the ultimate judgment regarding any specific care must be made by the clinician.[25] The Task Force could not reach a full consensus regarding the proposed approach for the treatment of CSA, mainly due to the different resources of each therapeutic centre, and taking into account that real-world conditions should be adapted to current guidelines. Following these considerations, the available treatment options were discussed, and a diagnosis and treatment algorithm was designed — Fig. 1. The starting point is the referral of patients with controlled and stabilized HF. If the diagnosis of central sleep apnea was performed with a level III sleep study, it is advisable to confirm it with a level I or II PSG as soon as possible. However, it is important to mention that although PSG I/II is considered the gold standard, it is not always easy to achieve, due to practical constraints, and results can take a long time to be obtained. If this is the case, CPAP can be used during the waiting period to PSG. Complementary diagnostic exams must include arterial blood gas analysis, brain natriuretic peptide (BNP), electrocardiogram, and echocardiogram with LVEF evaluation. If the results show an LVEF<45%, the patient evaluation by the Cardiology Department is mandatory. In this case, a new echocardiogram in stable conditions, myocardial scintigraphy, or myocardial magnetic resonance should be performed in selected cases, and the type of HF determined as ischemic or non-ischemic. If NYHA classes III or IV are identified, ASV is not recommended, and medical treatment should be optimized, with CPAP being a possibility for NYHA class III. In case the patient is in NYHA classes I or II, then the recommendations are indicated below.

Pressure adjustment

Titration should be performed during a full-night PSG titration or during daytime ventilatory adaptation. When positive pressure titration is not available within 2 weeks, and if the perceived risk of the continuing sleep apnoeas appears to inflict possible harm to the patient, we recommend a modified protocol of the CANPAP study.[26] In this case, fixed CPAP with a low pressure is applied and the pressure is increased in steps of 1-2, up to a maximum of 12 cm H_2O. Higher pressures can be considered individually but not higher than 13 cm H_2O due to hemodynamic changes. If CPAP is not effective, then other options have to be considered according to LVEF. We do not recommend a split-night study because of the limited titration period.

LVEF

- LVEF>45%: ASV is recommended, with an auto-EPAP pressure that should be set to the one that corrected the obstructive events. The respiratory rate should be automatic or 2 values below the rest value. The minimum support pressure should be zero, and the maximum should be 15 cm H_2O. If EPAP is titrated manually, it is important to mention that one must wait 10-20 minutes before increasing the EPAP pressure (1-2 cm H_2O), depending on the respiratory cycle time of the patient.
- LVEF between 30-45%: CPAP, with or without O_2, is recommended. ASV can be a possibility, considered on a case-by-case basis, in patients without CSR, who sign an informed consent and with medical agreement, as done in several studies.[8,12,14,27] Some members of the Task Force recommend that these cases should also be approved by the local ethical committee. If there is no consent, CPAP must be maintained, with pressures adjusted up to a maximum of 12 cm H_2O. Higher pressures can be considered in special situations, depending on the case. The Bilevel Positive Airway Pressure, Spontaneous/Timed might be an option only in normo/hypercapnic CSA related to HFrEF, if adequate trials of recommended therapies fail.
- LVEF<30%: For CPAP, Bilevel Positive Airway Pressure, Spontaneous/Timed, and oxygen therapy, the same treatment approach as for LVEF between 30-45% should be used. ASV is not recommended in these cases and should not be prescribed. Low flow oxygen therapy can also be an option. Low flow oxygen therapy has been used for decades in the treatment of central sleep apnea and CSR. It has been shown to decrease central sleep apnea and Cheyne-stokes respiration and is recommended by the American academy of sleep medicine. However, the long term effect of low-flow oxygen therapy on morbidity and mortality of HF patients with CSA/CSR is only currently under investigation in a prospective randomized controlled study.[28] Therefore, at present, it is not possible to give a conclusive recommendation towards this therapy.

Although new therapy modalities, such as the unilateral phrenic nerve stimulation, have shown promising results in recent publications,[29] the task force cannot at present make any recommendations regarding its use.

Follow-up

In cases of LVEF between 30-45% and <30%, there should be a tight control of the patient with frequent monitoring. After treatment initiation, follow-up should be performed in all patients (including those with LFEV>45%) with a cardiac ultrasound, between 1-3 months if LVEF>45% and 1 month if LVEF<45%. If the patient is treated with ASV, BNP levels and an echocardiogram should be performed after 3 months and every 6 months after that.

Final remarks

In conclusion, it is important to remember that in 2013-2014 ASV prescription was the rule, there was no treatment personalization, the methodology lacked importance. Currently, the opposite happens, with the prescription being too rigid due to the results of the SERVE-HF trial, regardless of its numerous flaws. In the future, a more unbiased culture must be adopted when some new treatment is released. Finally, a national registry of patients already exists, but it is not accessible, since the National Health Ministry does not release the data due to data protection. Also, the ADVENT-HF trial is being monitored every 6 months and it has not been stopped, suggesting there are no safety concerns. It is the authors' opinion that the implementation of the consensual algorithm hereby presented will aid in the clarification of treatment options and therefore help an increased number of patients who would benefit from ASV in Portugal.

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Conflicts of interest

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THEMATIC SERIES

How do I wean a patient with acute hypercapnic respiratory failure from noninvasive ventilation?

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KEYWORDS
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Abstract Noninvasive ventilation (NIV) has been increasingly used for the management of different etiologies of acute hypercapnic respiratory failure (AHRF). Although NIV implementation has been framed well by the guidelines, limited number of studies evaluated the NIV weaning strategies, including a gradual decrease in the level of ventilator support and/or duration of NIV as well as abrupt discontinuation, once respiratory acidosis and distress have resolved. None of the methods have yet been established to be superior to the other in terms of the success rate of weaning and duration of NIV; as well as mortality, length of stay (LOS) in hospital, respiratory ICU (RICU), and ICU. Patient-derived factors, such as etiology of AHRF, disease severity, history of prior NIV use, and clinical status can help to predict NIV weaning outcome and eventually choose the best method for each individual. In this paper, we have described the strategies for weaning a patient with AHRF from NIV and provided a quick guide for implementation of these data into daily practice based on our experience in and the current scientific evidence.

Clinical case

A 73-year-old female was hospitalized because of exacerbation of chronic obstructive pulmonary disease (COPD) with acute-on-chronic respiratory failure. She was cachectic (Body mass index: 18 kg/m^2), an ex-smoker (with a history of one-hundred-pack-years), on inhalers at home, and was using long term oxygen therapy (LTOT) for the last 3 years, but suboptimal (3 h/day on average). She had hypertension and cardiac arrhythmia with moderate functional limitation (i.e. short of breath with light activities and unable to perform two or more activities of daily living).

Abbreviations: ABG, Arterial blood gas; AHRF, Acute hypercapnic respiratory failure; COPD, Chronic obstructive pulmonary disease; EPAP, Expiratory positive airway pressure; ICU, Intensive care unit; IMCU, Intermediate care unit; IPAP, Inspiratory positive airway pressure; LTOT, Long term oxygen treatment; NMD, Neuromuscular disease; NIV, Noninvasive ventilation; OHS, Obesity hypoventilation; RR, Respiratory rate; AAA13, aaaaaa13; AAA14, aaaaaa14.
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On arrival to emergency department; she was started on noninvasive ventilation (NIV) because of her increased respiratory distress (accessory muscle use with RR: 30 bpm, HR: 120 bpm, Systolic/diastolic BP: 150/125 mmHg) and arterial blood gas result, revealing acute hypercapnic respiratory failure (AHRF) (pH: 7.29, PaCO2: 69 mmHg, PaO2: 54 mmHg, HCO3: 28 mmol/L, SatO2: 86% on room air). She was transferred to the respiratory ward to continue her management regarding COPD exacerbation and AHRF.

On admission day 2, the patient's clinical and gas-exchange status significantly improved (pH: 7.35, PaCO2: 61.6 mmHg, PaO2: 88.7 mmHg, HCO3: 29.6 mmol/L, SatO2: 97.7% on IPAP: 20/EPAP: 6 cmH2O, inspired oxygen fraction (FiO2): 0.28). We decided to wean the patient gradually off NIV.

Introduction

Noninvasive ventilation is effective in the management of different etiologies of acute hypercapnic respiratory failure (AHRF), especially for exacerbation and post-extubation weaning phase of COPD patients, as well as for palliative purposes.[1,2] The use of NIV in non-COPD causes of AHRF, such as acute decompensation of the obesity-hypoventilation syndrome (OHS) or neuromuscular diseases (NMD), has also been incorporated into clinical practice, although this has been based on mainly cohort studies.[2-4] On the other hand, NIV can also be utilized for the management of acute hypoxemic respiratory failure; including immune-compromised patients, post-operatively, patients with acute cardiogenic pulmonary edema, or Covid-19 pneumonia.[1,5,6]

Although NIV implementation for the management of AHRF has been framed well by the guidelines,[1,2] the strategies for weaning from NIV have not been well-defined yet. Most of the time, clinicians decide on NIV weaning intuitively according to their expertise and daily clinical practice. Unnecessarily prolonged use of NIV can lead to increased morbidity and even mortality, due to complications, including facial skin lesions or NIV-related pneumonia, as well as to the increased duration of hospitalization and cost.[7-12] Attempting extubating a patient as soon as he/she recovers from the primary disorder leading to respiratory failure is recommended to decrease complications associated with intubation[13]; similarly, NIV should be stopped as soon as the acute episode is has passed.[2] On the other hand, premature discontinuation of NIV can also result in worsening of respiratory status, with possible reinstitution of NIV. This risk might be extremely likely, especially in patients with a high risk of nocturnal hypoventilation (i.e. partial arterial pressure of carbon dioxide increase during sleep $>$10 mmHg), such as severe COPD, OHS, NMD, or chest wall disorders.[4,14,15] Keeping all of these important physiological points in mind, here is the critical question: When is the best time for weaning from NIV for whom?

Despite the wide range of studies available on weaning from invasive mechanical ventilation;[13,16,17] few numbers of studies have evaluated the NIV weaning strategies in patients with AHRF, especially with COPD.[18-27] Once the patient's general condition improves, NIV can be discontinued either by the patient (e.g. NIV intolerance) or by the physician (based on clinical findings, such as normalization of pH as well as respiratory status) or by protocol. In comparison to physician-directed weaning, protocol-directed discontinuation of NIV can reduce the duration of NIV and ICU stay as well as the mortality.[18,19,28] The strategies for weaning can be currently grouped into three, including a gradual decrease in the level of ventilator support and/or duration of NIV as well as abrupt discontinuation.[2,20-24,29] The 2016 BTS/ICS guidelines state that NIV can be discontinued in AHRF due to exacerbation of COPD, by reducing the daytime periods of ventilation in 2 to 3 days, based on clinical criteria, before being discontinued overnight.[2] Stepwise decrease in NIV duration, as recommended,[2] was shown to have no difference in NIV withdrawal success rates compared to abrupt discontinuation of NIV,[21,22] except for a longer intermediate care unit stay.[22] Similarly, in a recent RCT performed on 90 COPD patients, the success rate of weaning was similar between abrupt discontinuation, stepwise decrease in ventilator support level, and stepwise decrease in NIV duration arms; although the duration of NIV use and length of hospital stay were lower in first two groups.[23] Therefore, abrupt removal of NIV can be an acceptable option for spontaneously breathing patients of COPD, whereas the clinical status and disease severity can alter the physician's choice.

For non-COPD patients recovering from an episode of AHRF, a referral to a home ventilation service for assessment of 'domiciliary NIV use' has been recommended, while continuing 'nocturnal NIV' till to the accomplishment of the evaluation.[2] The presence of ongoing respiratory failure, in-hospital stability of NIV, and local care pathways can affect the decision on the location and timing of this assessment.[30] Recently, hospital discharge with positive airway pressure management was shown to reduce mortality in patients with OHS or suspected of having OHS.[31]

Patient-derived factors [such as etiology of AHRF (such as COPD vs. non-COPD causes), disease severity, history of prior NIV use, clinical status (for example rapid shallow breathing index (RSBI), bicarbonate level or pH$<$7.35 just before weaning] can help to predict NIV weaning outcome and eventually to choose the best method for each individual.[23,24,26,27] In the sole multicenter RCT, including both COPD and non-COPD patients, all three tested strategies were similarly effective in terms of NIV weaning success; while the presence of restrictive respiratory disorder due to obesity as an underlying lung disease was a predictor of failure, in contrast to COPD as a predictor of success (unpublished data under review).[24] In the future, additional research is required on weaning strategies/processes in non-COPD patients.

It is essential to decide the timing and methodology of NIV discontinuation after recovering from AHRF in adults, to improve patient outcomes. In this context, we aimed to describe and discuss the course of weaning and various weaning protocols, based on the most recent available literature and our experience both on COPD and non-COPD populations. Thereby, a practical guide for daily practice was intended.

When to start weaning from NIV in a patient recovering from AHRF?

The process of liberating patients from NIV generally referred to as weaning, should be planned as soon as the patient is initiated on NIV. The optimal timing for initiation

of weaning is as important as the methods of NIV discontinuation. These can differ based on the underlying etiology of AHRF (COPD vs. non-COPD) and the severity of the disease.

The 2016 BTS/ICS guideline states that discontinuation from NIV can be planned in AHRF due to acute exacerbation of COPD, in whom NIV is successful (pH $\geq$7.35 achieved, resolution of underlying cause and symptoms, respiratory rate normalized) following the first 24 h or longer duration on NIV[2]. Patients can be screened daily by the physician or respiratory therapist for the clinical criteria to be met before the weaning attempt, as summarized in Table 1.[22-24,29] If patients pass the baseline screening criteria, they can be discontinued from NIV onto nasal/Venturi oxygen at the minimal level (maximum of 5 L/min) to achieve the same oxygenation targets of NIV. If they also pass the re-assessment criteria after 1-4 h of spontaneous breathing with supplementary oxygen, the weaning process can be initiated. While pH>7.35 was mostly used as criteria, two of the studies used pH>7.30 as cut-off for screening.[18,26] However, a recent study[27] pointed pH<7.35 before weaning as a predictor of weaning failure. The physicians should keep in mind that more liberal criteria can increase the chance of earlier weaning with reduced rate of NIV complications and the duration of NIV and hospital stay; while stricter criteria can lead to a greater rate of withdrawal success, as in the case of extubation.[31]

Chronic obstructive pulmonary disease patients with persistent hypercapnia after recovering from AHRF have a poor prognosis with high rates of readmission and mortality within one year.[32] Actually, a relevant proportion (25%) of COPD patients in GOLD stage 3 and 4 exhibits chronic hypercapnia.[14] The long-term domiciliary NIV treatment can improve daytime hypercapnia and admission-free survival with no to little benefit in quality of life of those patients.[33] 'Normalization of PaCO2' has been recommended previously, for the COPD patient to be weaned off NIV,[2] indirectly increasing possibility of initiation of long-term NIV in hospital. However, based on emerging evidence, currently, reassessment for 'long-term NIV' has been suggested at 2−4 weeks after resolution, since nearly one fifth of the patients are no longer hypercapnic by then.[34-36]

Once non-COPD patients (such as exacerbation of NMD or OHS) or COPD patients with suspected or known sleep apnea syndrome have achieved clinical stability and the underlying cause of exacerbation has resolved, consideration can be given to in or outpatient assessment of OHS or overlap syndrome as well as domiciliary use of NIV, which can reduce mortality.[30,34] These patients cannot be weaned off NIV and may require in-hospital continuation and transition to long-term NIV, as suggested by home ventilation services.[2,34]

How to wean the patient from NIV?

Although NIV implementations for AHRF due to different etiologies have been described in detail,[1,2] the weaning methodology has not been well-defined yet by the guidelines. There are different weaning protocols recommended for invasive mechanical ventilation;[13,16,17] however, there have been no definitive recommendations for NIV weaning published in global guidelines yet,[1,2] except for Spanish and Indian guidelines.[29,37] Monitoring PaCO2 on and off NIV can be a useful guide for the withdrawal process,[2] in addition to other clinical parameters, including vitals, pH, and SatO2 levels. Patients can be considered as 'weaning failure'; if NIV reinstitution or intubation criteria[19,38,39] (Table 2) are met during the weaning phase/ right after NIV discontinuation, or if weaning is not possible. The time to define whether weaning is successful or not varies among studies from 2 to 8 days, the most common threshold being 3-5 days (Table 1).

Protocol-directed versus physician-directed weaning

NIV has generally been withdrawn depending on either by decision of the physician based on clinical findings with gas exchange status, or by the patient's demand (such as in NIV intolerance). On the other hand, the weaning can be protocolized. Duan et al compared those two strategies in 73 patients with COPD using NIV>24 h for AHRF.[18] In the protocol-directed arm, patients passing daily screening for NIV weaning criteria were discontinued by respiratory therapists from NIV directly onto oxygen with a nasal cannula till the patient was discharged. If the patient's clinical condition

Table 1 Clinical criteria for readiness to be weaned off NIV.[20, 22-25,29]

Baseline *(under NIV use)*	After 1-4 hour of spontaneous breathing *(with supplementary oxygen)*
pH $\geq$7.35	pH$\geq$7.35
Decrease from initial PaCO2 (at NIV start)$\geq$10%	Increase of PaCO2$\geq$ 20 % of baseline
PaO2>60 mmHg, PaO2/FiO2>150, or SaO2$\geq$90% on FiO2<50%	SaO_2 $\geq$88-92% with a $FiO_2\leq$40%
RR < 25-30 bpm	RR 8-30 bpm
HR 50-120 bpm	HR 50-120 bpm
Systolic BP 90-180 mmHg without vasopressors	Systolic BP 90-180 mmHg without vasopressors
Body temperature 36-38°C	Body temperature 36-38°C
Neurologic score of Kelly$\leq$ 2 (i.e. Alert. Follows simple,3-step complex commands)	Kelly score $\leq$2
No need for sedation	Absence of severe dyspnea (i.e. BORG>4)

BP: Blood pressure, *HR*: Heart rate *NIV*: noninvasive ventilation, *PaO2*: Partial arterial oxygen pressure, *RR*: Respiratory rate, *SaO2*: Oxygen saturation.

Table 2 Criteria for NIV re-institution or intubation.

NIV Re-institution	Intubation*	
	The major criteria	The minor criteria
RR <8 or >30 bpm Systolic BP <90 or >180 mmHg without vasopressors HR <50 or >120 bpm Neurologic score of Kelly >2 SaO_2 <90% with a $FiO_2 \geq 40\%$ pH<7.35 More than 20% increase in PaCO2 than the one recorded at start of weaning Presence of severe dyspnea (BORG>4).	Respiratory arrest Respiratory pauses with unconsciousness Severe hemodynamic instability Intolerance leading to discontinuation of the device.	Reduction ≥30% of basal PaO2/FiO2 ratio Increase of ≥20 % of PaCO2 Worsening of alertness based on the Kelly scale (≥1 point) New onset or persistent respiratory distress Exhaustion Secretion accumulation despite the use of aggressive physio-therapy and cough assist.

BP: Blood pressure, *FiO_2*: Fraction of inspired oxygen, *HR*: Heart rate *NIV*: noninvasive ventilation, *PaO2*: Partial arterial oxygen pressure, *RR*: Respiratory rate, *SatO2*: Oxygen saturation.

* The presence of one major criterion or two minor criteria for at least 1 h was considered indicative of the need for intubation, as previously reported.[19,38,39]

worsened as given in the protocol, NIV was reinstituted with daily screening to wean. By this method, the authors showed that NIV duration (-1.8 days) and length of ICU stay (-2.3 days) decreased as compared to the physician-directed method. Reduction in 28-day mortality was also shown as a benefit of protocols.[19] Accordingly, NIV weaning using a standardized protocol can provide better outcomes, with the prevention of prolonged NIV use due to an unplanned approach.[28]

Weaning strategies

There are few studies regarding methods of weaning from NIV.[22-24] Based on these studies, the strategies can be grouped into three (Table 3):

a) A gradual decrease in duration of NIV

Weaning can be started with the liberation of the patient from NIV during the daytime and then nighttime support can be gradually reduced. It has been recommended as such by BTS/ICS guideline,[2] which stands on a randomized trial designed by Plant et al. to compare the effect of NIV and standard medical treatment among patients with acute exacerbation of COPD, but not comparing different methods of NIV withdrawal.[40] Cuvelier et al.[41] gradually decreased duration of daytime NIV first, with close monitoring of clinical and ABG findings, in non-COPD patients (n=58) and COPD (n=42). When daytime NIV was stopped, the possibility of stopping nocturnal NIV was then assessed, on the basis of the patient's clinical condition and ABG values at the end of the following day. Inability to stop NIV for at least eight consecutive days (after two attempts) because of worsening clinical status, a rise in PaCO2 with respiratory acidosis (pH ≤7.35) and/or recurrent AHRF without any identifiable cause was considered as long-term NIV dependency, which was observed more frequently in non-COPD group (39 vs. 19%, respectively). Damas et al used a similar approach in a prospective cohort study, including 78 patients with acute exacerbation of chronic respiratory failure.[20] All of the patients were weaned successfully with a shorter duration of NIV use, compared to prior studies. But authors suggested other less time-consuming strategies.

b) A gradual decrease in ventilator support levels and duration of NIV

Another way of weaning from NIV could be a gradual decrease in ventilatory support with periods of spontaneous respiration. Nava et al used NIV as a weaning method for intubated COPD patients failing T-piece trial.[42] The authors gradually decreased the level of pressure support by 2 or 4 cmH2O per day in patients with hypercapnic ARF, who were successfully weaned from INV onto NIV, as long as they tolerate. They also allowed patients to breathe spontaneously with increasing duration. At the end of 3 h of spontaneous breathing if the patient's clinical condition and ABG findings are stable, patient was considered to be weaned off successfully. Moretti et al used the similar NIV weaning method with gradual decrease in pressure support and PEEP values in their study searching for incidence and causes of late NIV failure, recognition of which is critical since prolonged application of NIV can delay the time of intubation, leading to very poor prognosis.[43] While the inspiratory pressure support can be reduced by 2-4 cmH2O every 4-6 h with vitals and blood gas monitoring till IPAP<8 and EPAP<4 cmH2O to withdraw completely;[23] this reduction can also be supported with a concomitant decrease in duration of NIV use.[29]

c) Abrupt discontinuation of NIV

As the patient meets the weaning criteria, NIV can be stopped at once. Lun et al reported no significant difference in NIV withdrawal success rates between this strategy (25 patients) and a gradual decrease in NIV duration (35 patients) (56% vs. 74%, respectively, p=0.139).[21] The significant decrease in NIV duration (a median of 0 vs. 3 days, p<0.001)) was not reflected by the length of hospital stay.

Table 3 Weaning strategies.[24]

Gradual decrease in duration of NIV	In day 1, daytime (6 am-10 pm) maximum of 8 h, nighttime (10 pm-6 am) at least 6 h From day 2 NIV can be decreased at least 2 h/day each at the daytime and nighttime When a patient reaches the duration of NIV use as 4 hper 16 hduring daytime, without the presence of any reinstitution criteria, it can liberate definitively from NIV.
Gradual decrease in ventilator support levels and duration of NIV	In day 1, daytime maximum of 8 h, nighttime at least 6 h; from day 2 the daytime NIV decreased at least 2 h/day and nighttime discontinuation was considered similarly. The level of pressure support can be decreased by 2-4 cmH2O per 4 h during daytime, with no change at night time. If the patient deteriorates or cannot tolerate the change, the pressure support can be kept the same and the pressure support can be decreased the next day. When a patient reached to the level of PS of 8 cmH20, without the presence of any reinstitution criteria, it can liberate definitively from NIV.
Abrupt NIV discontinuation	Patients can be disconnected from NIV and oxygenated with a nasal cannula. Oxygen flow can be limited to a maximum of 5L/min.

The study was criticized as under-powered.[44] In a larger study by Sellares et al, no significant differences were reported in terms of weaning success, NIV dependency, 6-month hospital readmission, or survival between immediate withdrawal and 3 further days of nocturnal NIV, except for a shorter RICU stay (-1 day) in prior arm.[22]

Which strategy is better?

Comparison of a gradual decrease in duration of NIV or level of inspiratory pressure support with immediate withdrawal in 90 patients with COPD showed similar success rates for weaning; whereas the immediate withdrawal group had the lowest duration of NIV use and hospital stay as compared to the other two methods ($p=0.001$).[23] Recently, our group compared the above 3 strategies in a multicenter, multinational RCT including 197 patients with COPD and non-COPD causes.[24] The median duration of total NIV use after randomization and length of stay (LOS) in the intermediate care unit was shorter in the abrupt discontinuation group ($p<0.001$, and $p=0.044$, respectively), but this significant difference was lost after adjustments for variables differing between groups at the baseline. Rates of weaning failure and intubation, mortality, and domiciliary NIV prescription, as well as LOS in hospital were also similar between groups. As a conclusion, abrupt discontinuation can be feasible in clinically stable, spontaneously breathing COPD patients recovering from AHRF.[22-24,45] This recommendation was supported by 53% of recently published Spanish consensus members,[37] whereas the Indian guidelines recommend the adoption of any of the three strategies.[29]

High flow nasal cannula is a relatively new treatment that has been suggested as a complementary therapy during breaks off NIV.[46,47] It was associated with better comfort and improved respiratory rate and dyspnea compared to low flow oxygen, during NIV breaks.[47] It can shorten NIV duration and probably increase NIV weaning success in AHRF. High flow nasal cannula can be an alternative to NIV after partial reversal of respiratory acidosis, especially in patients not tolerating NIV with a potential to deliver bronchodilator treatment as well.[49] However, there is not sufficient evidence yet.[48-50]

Reasons for weaning failure

Monitoring clinical and physiological factors throughout this process can help the physicians to predict the outcomes, such as prevention of AHRF relapse after discontinuation, reducing the duration of NIV and hospital stay, complications, or mortality. On the other hand, the patient may not be weaned successfully and can get intubated and/or discharged on NIV.

Predictors of weaning failure can be listed as the presence of restrictive respiratory disorder due to obesity as underlying lung disease, severe functional limitation, history of prior NIV use, time spent on NIV, higher PaCO2 and lower pH at enrollment, HCO3 concentration, and a $pH<7.35$ before weaning, poorer Glasgow Coma Scale.[23,24,27] On the other hand; the presence of COPD as underlying lung disease, location of NIV initiation (wards and intermediate care unit as opposed to emergency departments and ICUs), rapid shallow breathing index (i.e. respiratory rate /tidal volume) just before NIV turned off <67.4 can predict weaning success.[24,26] As a result, those patients with bad prognostic factors (such as non-COPD cause of AHRF) should be monitored cautiously during the weaning period. Additionally patients on NIV can be followed up routinely with rapid shallow breathing index, for optimal timing of weaning.

Weaning failure can be associated with increased morbidity and mortality.[29] In the only real-life observational study for NIV weaning in AHRF due to COPD exacerbations, 39% of patients failed weaning with adaptation to domiciliary ventilation.[25] However, the timing of recovery of hypercapnia is crucial as mentioned above and is likely to have the most important impact on long term NIV. Reassessment of hypercapnia in 2-4 weeks after the initial episode is recommended for identifying patients who are most likely to benefit from

long-term NIV.[34,35] Non-COPD causes of AHRF (such as OHS or NMD) can require home ventilation services as mentioned above.[2] Despite no previous neurological history, it was suggested that NMD be investigated in patients difficult to wean from ventilator support.[51]

Continuation of the clinical case

Our patient passed the readiness criteria (Table 1) both on NIV and spontaneous breathing (with nasal oxygen 2lt/min). Since she had cardiovascular co-morbidities and functional limitation, she was started on weaning strategy of gradual decrease in ventilator support levels and duration of NIV. However, her clinical status declined on weaning day 2 with emerging fever, tachypnea, tachycardia, increased cough, phlegm and severe respiratory acidosis (pH 7.30). She was diagnosed with pneumonia, started on modified antibiotic regimen and continued back on NIV with increased pressure and duration. After 5 days of treatment, the patient passed again readiness criteria, and she was weaned off NIV successfully using the same strategy in 3 days. The patient was discharged on LTOT with an appointment for an assessment at 'home ventilation services' two weeks later, since she had hypercapnia without acidosis at discharge.

Conclusion

It is important to know the timing and methods of weaning from NIV for patients recovering from AHRF, since inappropriate discontinuation can result in increased morbidity and mortality. Clinical status and disease severity may play a part in choosing the best method. None of the methods have yet been clearly established to be superior to the others in terms of relapse of AHRF in COPD patients after liberation from NIV, as well as mortality and long-term ventilator dependence. Therefore, abrupt removal of NIV can be a better option for uncomplicated cases of COPD to decrease the rate of NIV complications, while any of the methods can be adopted based on the patient's characteristics. Last but not least; we need more robust evidence for alternative NIV weaning strategies in different patient subgroups with AHRF.

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LETTER TO THE EDITOR

Durability of COVID-19 vaccine induced T-cell mediated immune responses measured using the QuantiFERON SARS-CoV-2 assay

Dear Editor,

It is becoming increasingly evident that neutralizing antibodies as well as T-cell-mediated immune responses (acquired through natural SARS-CoV-2 infection or vaccination against the SARS-CoV-2 spike protein) are crucial to protect against COVID-19.[1-5] Evidence suggests that T-cell responses are required for durable immunity against COVID-19, including emerging SARS-CoV-2 variants of concern (VOC), and are implicated in reducing disease severity.[6] While VOC may partially escape the humoral response, functional preservation of vaccine-induced T-cells allows VOC recognition independent of timing or regimen.[3,7] Therefore, monitoring T-cell responses may provide a more comprehensive picture of COVID-19 immunity; however, data are limited on the magnitude and durability of T-cell immunity following two doses versus booster dose responses.

We previously carried out a feasibility study using the QIAreach™ Anti-SARS-CoV-2 Total Test (QIAGEN, Hilden, Germany) and QuantiFERON SARS-CoV-2 Research Use Only (QFN SARS-CoV-2) assay (QIAGEN, Germantown, USA) to measure durability of total antibody and T-cell-mediated responses, respectively, in 12 subjects during and after the 2-dose mRNA vaccination regimen (mRNA-1273 [Moderna]) and in 4 PCR-confirmed COVID-19 convalescent subjects.[8] We showed that vaccinated individuals had robust antibody and CD4+/CD8+ T-cell responses to a SARS-CoV-2 mRNA vaccine for 2 months following completion of the initial 2-dose regimen.[8] However, in most individuals, T-cell response declined between first and second doses, demonstrating the need for a second dose.[8]

Here, we report on the QFN SARS-CoV-2 testing in an expanded cohort of COVID-19-naïve, healthy volunteers to measure the durability of mRNA vaccine T-cell responses for up to 40 weeks following the initial 2-dose regimen (mRNA-1273 [Moderna] or BNT162b2 [Pfizer-BioNTech] vaccines), pre-booster, and post-booster (matched to their initial regimen; received at median 8.6 [range: 7.2—9.0] months after completing the initial vaccination regimen). To measure QFN SARS-CoV-2 T-cell response, whole blood specimens were collected from: 26 subjects at days 14—20 (2 weeks) following completion of the initial 2-dose vaccination regimen (mRNA-1273, n=13; BNT162b2, n=13); 24 subjects at days 182—252 (7—9 months; pre-booster dose) (mRNA-1273, n=13; BNT162b2, n=11); and 7 subjects up to 3 months post-booster. Details on plasma extraction were described previously.[1] The QFN SARS-CoV-2 assay consists of three antigen (Ag) tubes, SARS-CoV-2 Ag1, Ag2, and Ag3. The Ag1 tube contains CD4+ epitopes derived from the S1 subunit (receptor-binding domain) of the spike protein, Ag2 contains CD4+ and CD8+ epitopes from the S1 and S2 subunits of the spike protein, and Ag3 comprises CD4+ and CD8+ epitopes from S1 and S2, plus immunodominant CD8+ epitopes derived from the whole genome.[8] Reactive T-cell response was defined as an interferon-gamma (IFN-γ) value of $\geq$0.15 international units (IU)/mL greater than the background value from the QFN SARS-CoV-2 Nil tube.[3] Each QFN SARS-CoV-2 Ag Nil subtracted unpaired response was compared between vaccine types by Mann-Whitney test (2 weeks versus 7—9 months after the initial 2-dose regimen). Wilcoxon matched-pairs signed rank test was used to compare pre-booster and 3-month post-booster responses. Loss to follow-up was minor (n=9 at days 182—252 testing, comprising n=5/13 for mRNA-1273 and n=4/11 for BNT162b2); and there were no notable differences in clinical and demographic characteristics between those lost to follow-up versus other study participants at days 182—252.

We found no statistically significant differences in T-cell responses between subjects receiving the mRNA-1273 and the BNT162b2 vaccines at any timepoint (**Fig. 1**). Following completion of the initial 2-dose mRNA-1273 regimen, median Ag1, Ag2, and Ag3 IFN-γ values (Nil subtracted) were 1.1, 1.7, and 1.8 IU/mL, respectively; all subjects were classified as reactive. Upon completion of the durability study (median follow-up for mRNA-1273 regimen: 8.5 [range: 6.5—9.1] months), these values (Nil subtracted) were 0.27, 0.59, and 0.69 IU/mL, respectively; 11/13 (84.6%) subjects were reactive. Upon completion of the 2-dose BNT162b2 regimen, median Ag1, Ag2, and Ag3 IFN-γ values (Nil subtracted) were 0.68, 1.4, and 2.1 IU/mL, respectively; all subjects were reactive. After the median 7.2 [range: 6.6—9.4] months' follow-up for the BNT162b2 regimen, these values (Nil subtracted) were 0.18, 0.42, and 0.72 IU/mL, respectively; 8/11 (72.7%) subjects were reactive.

Compared with pre-booster levels, elevated Ag1, Ag2, and Ag3 responses were observed within 7 days after

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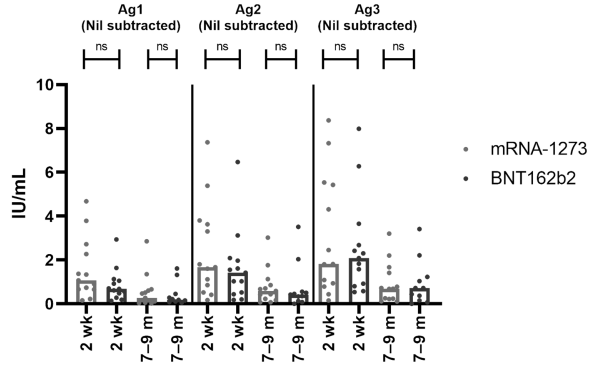

Fig. 1 Comparison of QFN SARS-CoV-2 antigen tube (Nil subtracted) T-cell mediated immune response in subjects receiving an initial 2-dose vaccination with the mRNA-1273 or BNT162b2 vaccines. A Mann-Whitney test was used to compare responses between vaccines at the 2-week and 7−9-month timepoints.
Dots represent individual test points and columns represent median responses within the test cohort. Not all subjects had specimens collected at all timepoints.
Ag, antigen tube; IU, international units; m: months; ns: non-significant; wk, weeks.

receiving a booster dose (mRNA-1273, n=6; BNT162b2, n=1), with IFN-γ levels increasing at 1 month post-booster but declining by 3 months (**Fig. 2**). At 3 months post-booster, there were no statistically significant differences between pre- and post-booster Ag1, Ag2, and Ag3 IFN-γ levels, regardless of vaccine.

In this longitudinal study, T-cell mediated immune responses were sustained for 9 months following the 2-dose mRNA vaccination regimen in COVID-19-naïve individuals, with no significant differences between vaccines. In response to a booster dose, T-cell responses initially increased before stabilizing to pre-booster levels 3 months post-booster.

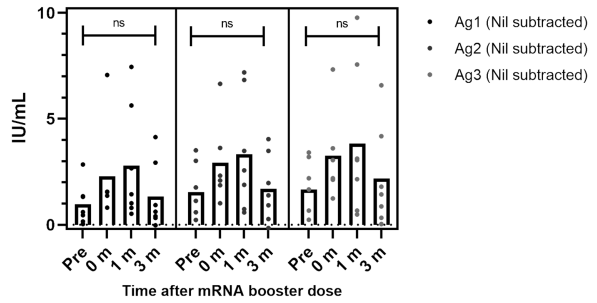

Fig. 2 Comparison of QFN SARS-CoV-2 antigen tube (Nil subtracted) T-cell mediated immune response in subjects pre- and post-booster vaccination (whole blood specimens collected at 0 months [≤7 days], 1 month [18−32 days], and 3 months [81−96 days] following the booster). Wilcoxon matched-pairs signed rank test was used to compare pre-booster and 3-month post-booster responses.
Dots represent individual test points and columns represent median responses within the test cohort. Not all subjects had specimens collected at all timepoints.
Ag, antigen tube; IU, international units; m: months; ns: non-significant.

This is one of the few longitudinal studies exploring the durability of cellular immunity generated in response to mRNA vaccines and providing insights into vaccine efficacy; even fewer longitudinal studies have investigated efficacy against VOC. A spike in antibody responses has been reported after booster vaccination but the durability of these responses is yet to be determined;[3] however, T-cell responses are generally maintained at pre-booster levels and potentially provide longer-term protection,[3] especially against severe disease as protective T-cell immunity may correlate with milder clinical manifestations.[1,3,5] Notably, this has implications for immunocompromised individuals who may be at risk of severe COVID-19 but have attenuated humoral responses to vaccination.[9] Gaining a better understanding of the cellular immune response to COVID-19 should be an important point of future research, in order to inform public health policies and guide targeted interventions for vulnerable populations.[6] Further research is also needed to investigate whether immune response monitoring can identify correlates of disease protection[5] or has a role in COVID-19 clinical management.

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Consent statement

All subjects provided informed consent. Study protocol and documentation were approved by an independent Institutional Review Board. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Author contributions

All authors made significant contributions to the work reported; took part in drafting, revising and critically reviewing the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflict of Interest

FS, NA, KC, PH, SR, and JH are employees of QIAGEN Sciences Inc. RA is an employee of QIAGEN SRL. DM and VN are employees of QIAGEN Manchester Ltd.

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LETTER TO THE EDITOR

Flow-controlled ventilation may reduce mechanical power and increase ventilatory efficiency in severe coronavirus disease-19 acute respiratory distress syndrome

To the Editor,

The prevention of ventilator-induced lung injury (VILI) is the mainstay of the management of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS).[1] Official guidelines have focused on tidal volume, plateau pressure (Pplat), positive end-expiratory pressure (PEEP), and driving pressure (DP), i.e., the difference between Pplat and PEEP, to identify lung-protective ventilation strategies.[2] However, even values of tidal volumes and Pplat that are normally considered safe may result in injurious ventilation.[3]

Mechanical power (MP) represents the total energy transferred from the mechanical ventilator to the lungs during inflation and includes dynamic variables such as inspiratory flow rate and breathing frequency.[3] Some studies suggest that MP may predict mortality in ARDS patients[3] and that higher inspiratory flow rates increase the risk of VILI in patients with mild to moderate ARDS.[4]

The lungs of patients with coronavirus disease (COVID)-19 related ARDS are characterized by parenchymal heterogeneity, leading to regional differences in pulmonary mechanical properties.[5] Consequently, higher velocities of lung inflation may drive a greater fraction of tidal volume to alveolar units with shorter time constant and unevenly amplify lung stress in some regions.[3] Therefore, reducing flow rates might be beneficial.

Flow-controlled ventilation (FCV) (Evone®, Ventinova Medical, Eindhoven, The Netherlands) is a ventilatory mode where both inspiratory and expiratory flow rates are maintained constant and $<$ 20 L/min throughout the respiratory cycle by regulating tracheal pressure, as measured through a dedicated lumen opening at the distal end of the endotracheal tube.[6] During FCV, the inspiratory flow rate, inspiratory to expiratory ratio, peak inspiratory pressure (Ppeak), end-expiratory pressure (EEP), and the inspiratory concentration of oxygen are pre-set, whereas tidal volume and respiratory rate vary depending on ventilator settings and the patient's respiratory mechanics.[7] Some studies observed improved lung recruitment, more homogeneous lung aeration,[6,8,9] better gas exchange,[8-12] and attenuated experimental lung injury with FCV,[12,] compared to volume-targeted mechanical ventilation (conventional mechanical ventilation, CMV). We hypothesize that FCV would reduce MP and ventilatory ratio (VR) in COVID-19 patients developing refractory hypoxemia despite optimization of CMV and prone positioning.

This pilot study was performed in 10 sedated and paralyzed COVID-19 ARDS patients admitted to the intensive care unit with arterial partial pressure of oxygen to inspired oxygen fraction ratio (PaO2/FiO2) $<$ 150 mmHg during CMV while in prone position for at least 12 consecutive hours.[2] Inspiratory and expiratory flow rates were initially set at 15 L/min with inspiratory to expiratory ratio 1:1, while EEP was equal to PEEP and Ppeak to Pplat during CMV, thereby maintaining approximately the same DP and consequently similar tidal volumes. All measurements were obtained in CMV prior to switching to FCV (CMV1), after 4 hours of FCV, and then again after 4 hours of CMV (CMV2). All variables are reported as median (interquartile range) and compared using the Friedman test, followed by pairwise comparison with Wilcoxon signed-rank test and *post-hoc* Bonferroni correction. All statistical tests were two-tailed and statistical significance was defined as $p<0.05$.

Patient age was 59 (55-57) years and the predicted body weight 65 (59-68) kg. Nine (90%) patients survived the hospital stay. As reported in Table 1, during FCV inspiratory flow rate, respiratory rate, and minute ventilation were all decreased, compared to both CMV1 and CMV2. During FCV the MP was 10.8 (9.9-13.4) J/min, as opposed to CMV1 [22.7 (20.3-25.6) J/min (p=0.006)] and CMV2 [20.1 (19.0-24.0) J/min (p=0.006)], and VR was 1.40 (1.28-1.44), as compared with CMV1 [2.22 (1.90-2.56) (p=0.006)] and CMV2 [2.20 (1.79-2.57) (p=0.006)]. Arterial partial pressure of carbon dioxide, pH, and PaO2/FiO2 were not significantly different among the three conditions.

Our study evaluating a series of 10 consecutive patients affected by COVID-19 with refractory hypoxemia, despite prone positioning while receiving CMV, suggests that FCV may be associated with some advantages. First, the application of FCV resulted in decreased MP, as a consequence of lower inspiratory flow rates and breathing frequencies, potentially reducing the dissipated energy.[7,12,13] Indeed, FCV was shown to reduce MP[11] and attenuate VILI through

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Table 1 Ventilatory settings, mechanical properties of the respiratory system, and outcome variables

Variable	CMV1	FCV	CMV2	p-value[a]	Kendall's W
Ventilatory settings					
Respiratory rate (breaths/min)	26 (24-28)	17 (16-18)[b,c]	25 (22-26)	<0.001	0.930
Tidal volume (mL/kg PBW)	6.9 (6.8-7.3)	6.8 (6.5-7.3)	6.8 (6.5-7.2)	0.968	0.003
Minute ventilation (L/min)	11.8 (10.2-12.8)	7.7 (7.1-8.2)[d,e]	10.8 (9.6-12.1)	<0.001	0.830
Peak pressure (cmH_2O)	27 (25-28)	23 (20-25)[b,c]	26 (25-28)	<0.001	0.810
Plateau pressure (cmH_2O)	21 (20-23)	21 (19-23)	22 (21-23)	0.015	0.420
PEEP (cmH_2O)	9 (8-10)	9 (7-10)	9 (8-10)	0.772	0.030
Inspiratory flow (L/min)	26 (23-26)	15 (14-15)[d,e]	22 (22-26)	<0.001	0.800
Gas exchanges					
pH	7.37 (7.30-7.42)	7.39 (7.36-7.42)	7.34 (7.27-7.42)	0.280	0.130
$PaCO_2$ (mmHg)	49 (43-51)	45 (42-48)	51 (45-56)	0.275	0.130
PaO_2/FiO_2 (mmHg)	128 (116-134)	136 (115-147)	134 (106-152)	0.275	0.150
Ventilatory ratio	2.22 (1.90-2.56)	1.40 (1.28-1.44)[d,e]	2.20 (1.79-2.57)	<0.001	0.770
Mechanical properties of the respiratory system					
Crs (mL/cmH_2O)	36 (34-38)	35 (34-40)	36 (33-39)	0.704	0.040
Driving pressure (cmH_2O)	13 (12-13)	12 (11-13)	13 (12-14)	0.331	0.110
Mechanical power (J/min)	22.7 (20.3-25.6)	10.8 (9.9-13.4)[d,e]	20.1 (19.0-24.0)	<0.001	0.760

Abbreviations: CMV, conventional mechanical ventilation; FCV, flow-controlled ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2/FiO_2, arterial partial pressure of oxygen to fraction of inspired oxygen ratio; Crs, compliance of the respiratory system.

All measurement were obtained in CMV prior to switching to FCV (CMV1), after 4 hours of FCV, and then again after 4 hours of CMV (CMV2). During CMV, plateau pressure (Pplat) and total PEEP were measured at the points of zero flow during an end-inspiratory and end-expiratory pause, respectively, while during FCV Pplat is displayed every 10 cycles after an automatic pressure drop in the pressure curve. Driving pressure was computed as the difference between Pplat and total PEEP, during CMV, and the difference between peak pressure (Ppeak) and end-expiratory pressure, during FCV. Crs was calculated as the ratio between tidal volume and driving pressure. Inspiratory flow during CMV was calculated as the ratio between tidal volumes and inspiratory time, while inspiratory flow during FCV is set on the ventilator.

Ventilatory ratio was calculated as the ratio between the product of measured minute ventilation (mL/min) and measured PaCO2 and the product between predicted minute ventilation (PBW*100 mL/min) and expected PaCO2 (37.5 mmHg) (10.1164/rccm.201804-0692OC). Mechanical power was calculated as follows: 0.098*respiratory rate*tidal volume*[Ppeak-1/2*(Pplat-PEEP)] (10.1186/s13054-020-03116-w).

Variables are reported as median (interquartile range) and were compared using the Friedman two-way analysis of variance, followed by pairwise comparison with Wilcoxon signed-rank test and *post-hoc* Bonferroni correction, when indicated. The Kendall's W value is the effect size estimate for Friedman test and ranges from 0.1-0.3 (small effect) to >0.5 (large effect).

[a] p-value from the Friedman two-way analysis of variance.
[b] $p<0.05$ between FCV and CMV1 after *post-hoc* Bonferroni correction.
[c] $p<0.05$ between FCV and CMV2 after *post-hoc* Bonferroni correction.
[d] $p<0.01$ between FCV and CMV1 after *post-hoc* Bonferroni correction.
[e] $p<0.01$ between FCV and CMV2 after *post-hoc* Bonferroni correction.

this mechanism in porcine models.[12] Second, our results are in keeping with preclinical[8,9,12] and clinical studies,[6,] demonstrating higher ventilatory efficiency, probably related to improved intrapulmonary distribution of ventilation with FCV. Third, although we did not observe any significant improvement in gas exchange with FCV, previous studies reported better oxygenation and carbon dioxide elimination with this mode.[8-12,] Therefore, our study extends to the critical illness setting the current evidence, mainly limited to preclinical studies and small clinical studies performed in the operating room, suggesting that FCV might reduce VILI, while maintaining adequate gas exchanges.

Our study has important limitations. First, the small sample size makes our findings exploratory and hypothesis-generating. Larger prospective studies are necessary to confirm these results and support clinical studies ascertaining the impact of FCV on clinical outcomes. Second, the external validity and the generalizability of our findings to patients with acute respiratory failure of different etiology need to be assessed. Furthermore, we cannot rule out that different dead space of the ventilator apparatus may have contributed to the improvement of VR with FCV. However, this is unlikely because we always used an active humidifier before the Y-piece of the respiratory circuit during CMV.

In conclusion, FCV reduced MP and VR in a small cohort of severely hypoxemic COVID-19 patients receiving CMV and prone positioning.

Authors' contributions

Conception and design of the study: AG, TP. Acquisition of the data: AG, FB, RC. Analysis of the data: AG, TP, NS. Interpretation of the data: all authors. Drafting of the manuscript: AG, TP, NS, PN. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the version to be submitted: all authors.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

PN research lab received grants/research equipment by Draeger, Intersurgical SPA, and Gilead. PN receives royalties from Intersurgical SPA for Helmet Next invention. He also received speaking fees from Getinge, Intersurgical SPA, Gilead, MSD, Draeger, and Medicair. PN has no conflict of interest to declare in relation to this manuscript. The other authors have no competing interests to declare.

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Ethics approval and consent to participate

The study was approved by the Local Ethical Committee (Comitato Etico di Sperimentazione Clinica ULSS 2 Marca Trevigiana, protocol n. 0235105/21) and was conducted in accordance with the principles of the Helsinki Declaration. Informed consent was obtained according to the national regulation.

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LETTER TO THE EDITOR

How COVID-19 changed our bronchoscopy procedures: A comparison with the Portuguese Pulmonology Society Recommendations

Facing COVID-19 had led the world to face many challenges to limit the spread of the virus and to minimize the risk of saturation of health facilities and intensive care beds. Each country had to consider its epidemiological and economical context, as well as scientific data (variable and evolving scientific knowledge, national and international experts' opinion, and official declarations of the world health organization).

Morocco has taken proactive and effective early decisions namely the general lockdown and the maintain of minimal activity including medical activity. The challenge was to guaranty the access of care and treatment for urgent patients as highly suspected cancer patients. Since lung cancer is known by its delay to diagnosis and its reduced prognosis outside any pandemic situation, we decided to maintain our protocols of care for all patients suspected with lung cancer as needed while changing our bronchoscopy procedures and implementing safety measures.

Bronchoscopy is an aerosol generating procedure with high risk of transmission and contamination.[1] To protect both health care workers and patients, we sought to strictly implement relevant standards for preventing from infections by adapting available resources. We were inspired by several guidelines and recommendations regarding bronchoscopy that were published at the beginning of the pandemic. These were expert opinion derived from observations made during prior respiratory viral outbreaks.[2—6] As the situation evolves, new documents aiming to guide interventional pulmonology were published. The consensus statement for interventional pulmonology from the Portuguese Pulmonology Society provided a set of recommendations and a thorough overview.[7]

How Covid-19 changed our bronchoscopy procedures? In the first three months of declared pandemic, bronchoscopy was essentially limited for highly suspected cases of lung cancer that had no alternate option i.e., percutaneous lung biopsies, pleural biopsy, suspected metastatic site or peripheral lymphadenectomy biopsy. Bronchoscopy was postponed for patients with no urgent situation. All the patients had to be asymptomatic within 2 weeks (they were asked about symptoms, contacts and travel history). Note that only 10% of the patients had a COVID-19 PCR test performed at this time. The bronchoscopy unit was considered as a high-risk area with limited access, we reduced personnel to one doctor and one nurse performing bronchoscopy and patients were scheduled with different appointment times (1h30 min between each patient). Upon arrival, we checked the temperature of both the patient and his/her accompanying caregiver or relative (limited to one per patient), using non-contact thermometer before being allowed to enter the bronchoscopy area in the attending room with a medical mask put on. A specific place to store, to gown and to remove all items required for personal protective equipment (PPE), according to hospital protocol and standards, was defined close to the procedural suite. For operators (doctor and nurse), the use of an FFP2 (filtering facepiece) respirator was mandatory while performing bronchoscopy as well as disposable gowns and gloves, hoods, boots and face shields.[8]

Bronchoscopy and anesthesia precautions: All patients were under spontaneous ventilation. Oxygen supplementation was done, when needed, through a nasal cannula. Bronchoscopy was performed with local anesthesia as we do in the most cases. We performed flexible bronchoscopy with a transnasal approach. To minimize droplet emission and to reduce the risks of virus aerosolization, we performed a hole in the patient's medical mask where we introduced the bronchoscope, whenever feasible and tolerable for the patient. If not, the medical mask was placed over the patient's mouth. The time of performed procedures was reduced to the shortest possible and with the fewest number of sampling procedures required to achieve the clinical goal.[9] At the end of the exam, surfaces of the endoscopy room were carefully cleaned and disinfected following the disinfection policy. A high-level manual disinfection when using a fiberoptic bronchoscope or an automated endoscope reprocessor when using a video-bronchoscope was realized by the nurse with the supervision of the doctor. The room was ventilated with natural ventilation for at least 45 min after the end of the procedure as a negative pressure room wasn't available throughout the department. All specimens were manually delivered in a dedicated box.

With the extension of screening and detection of coronavirus, the implementation of codified infection control measures and procedures in the endoscopy unit, a second bronchoscopist was assigned to perform the exam with an

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increase of patients' recruitment (namely previously postponed patients) starting from the 15th of June 2020.

On early august 2020, the consensus statement for interventional pulmonology from the Portuguese Pulmonology Society was published.[7] These recommendations comforted us on pursuing our strategy given the similarities especially keeping a well-organized endoscopy unit (administrative issues, physical space preparation) and considering all patients as infected and therefore, contact precautions were a critical point to master (cleaning and disinfecting patient care equipment and operating room, personal protective equipment, safety rules for staff and patients). As stated in this guidance, individual clinical judgment and local resources may lead to alternative perspectives.[7] For example, a negative pressure room wasn't available throughout our department neither a natural ventilation with airflow and duration of at least 160 L/s and 30 min as recommended. Instead, a natural ventilation for 45 min at least after the end of the procedure with all the windows open to create a natural air flow was realized in our operating room associated to rigorous cleaning and disinfection of the patient care equipment and surfaces.

With the launch of rapid screening tests for COVID-19 in the late of November 2020, performing a PCR or rapid antigenic screening for all the patients was then mandatory 24 to 48 h before the scheduled bronchoscopy. Bronchoscopy Protocols Enacted for COVID-19 were maintained despite a negative tests result.[10] We recovered since then the full activity of the bronchoscopy unit with 4 bronchoscopists and recruited as much patients as before the world pandemic.

In total, our activity in the endoscopy unit decreased by 40% in the first year since the beginning of the pandemic (421 bronchoscopies performed from Mars 2019 to February 2020 versus 252 from Mars 2020 to February 2021). Then we registered an increase in the next year with 402 bronchoscopies performed from Mars 2021 to February 2022 that is 95% of the activity compared to the year before the pandemic.

No outbreaks occurred within the staff and no patients were known to have developed COVID-19 after a procedure during 2 years since declared pandemic in our country (March 2nd, 2020, until March 1st, 2022). Indeed, no COVID-19 symptoms were developed among health workers (in total 4 doctors and 2 nurses). For patients that underwent bronchoscopy, they were either still hospitalized for at least 1 week after the procedure, either seen on consultation 2 weeks later. They were asked about symptoms and a PCR or rapid antigenic tests were realized when COVID-19 was suspected (9 hospitalized patients, tests negatives).

Bronchoscopy is considered with high risk of transmission and contamination and could appear scary to perform especially at the beginning of the pandemic where the safety of this procedure was questioned, where scientific knowledge about the COVID-19 was weak and where PCR tests were performed at this time to just few patients. But, as many remarkable healthcare workers throughout the world, we believed in the concept of optimizing resources, using correctly protective equipment, focusing on core values, fulfilling and honouring the Hippocratic Oath. Our main goal was to develop an adapted strategy in a context of evolving reorganization of procedures according to the evolution of the epidemiological situation, scientific knowledge and advances, the availability of diagnostic means and local resources. This guarantied the safety of both health care workers and patients without impacting the quality of our healthcare services and guarantied the access of diagnostic procedures without delays to all highly suspected lung cancer patients.

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Declaration of Competing Interest

The Authors declare that there is no conflict of interest

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LETTER TO THE EDITOR

Benign metastasizing leiomyoma presenting as multiple pulmonary nodules: A radiological-pathological correlation

Dear editor,

Incidental pulmonary nodules are a diagnostic challenge for both radiologists and pulmonologists.

We report a case of a 47-year-old female, with invasive oral squamous cell carcinoma of the tongue, that presented with multiple bilateral peri centimetric pulmonary nodules revealed on a Cervicothoracic Computed Tomography (CT) scan, requested for tumor staging. The patient underwent hemiglossectomy and was referred to our Pulmonary Oncology clinic.

Clinical evaluation revealed a one-month history of non-productive cough and dyspnea with moderate effort, as well as an exposure to parakeets for about 3 months. She was a non-smoker and denied hemoptysis, recent weight loss, fever, or any other constitutional symptoms. Bronchofibroscopy showed no signs of endobronchial malignancy and bronchial aspirate was amicrobial. Transthoracic biopsy was

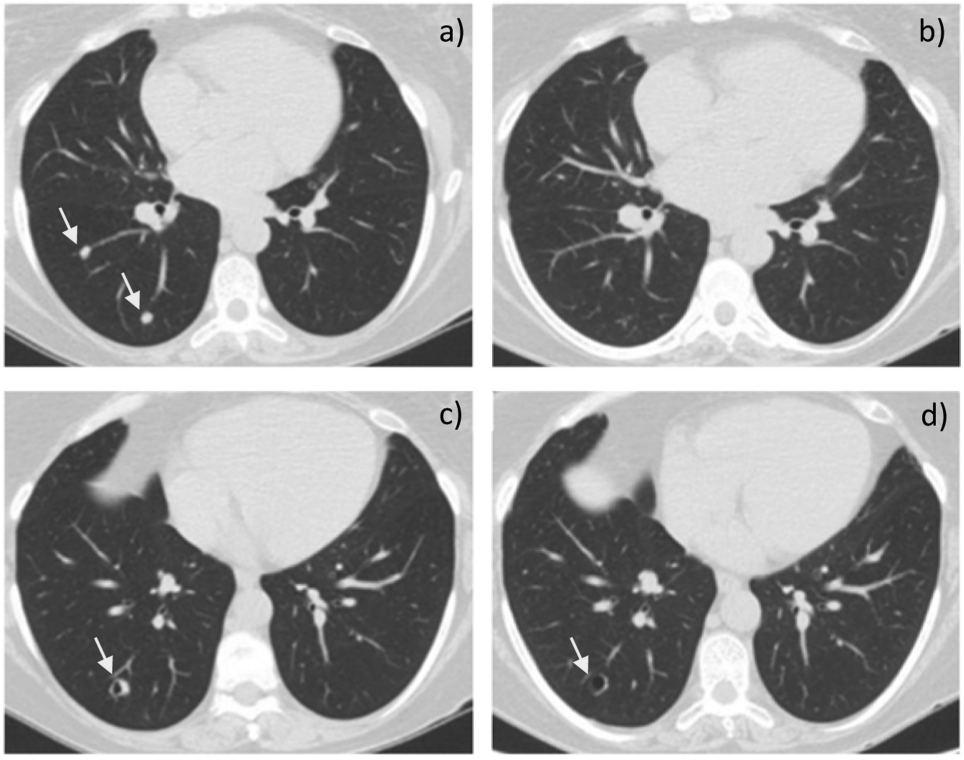

Fig. 1 (a—d): Computed tomography axial images at middle (a, b) and lower lung (c, d) before (a, c) and after hysterectomy (b, d). The patient presented multiple bilateral well-defined and non-calcified lung nodules with a centrilobular distribution (arrows in a; nodules on the left not shown). During follow-up, nodules varied in size, and some developed cavitation (arrow in c). There was no interstitial lung disease, cystic lesions, pleural effusion, or mediastinal lymphadenopathy. After hysterectomy, some nodules completely disappeared (b) and cavitated nodules lost their solid component (arrow in d).

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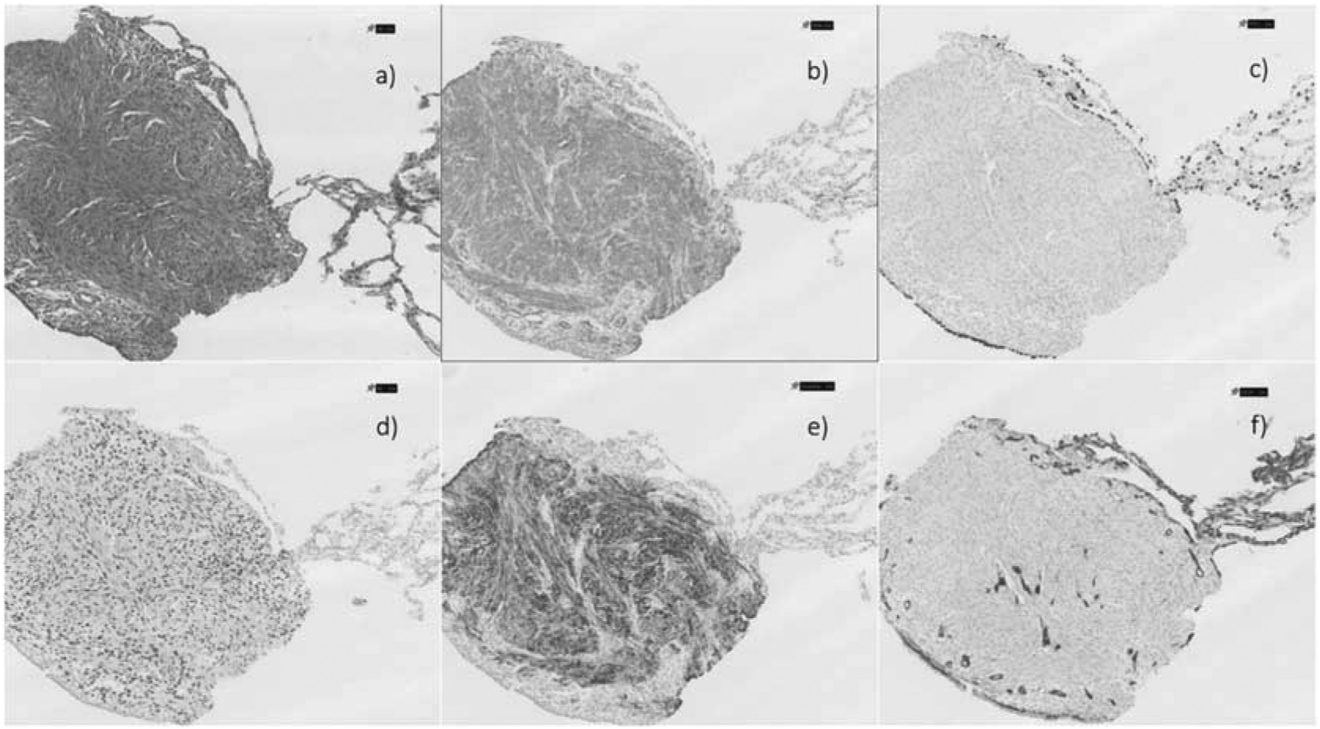

Fig. 2 (a—f): Pulmonary nodule transthoracic biopsy - BML lung lesions consist of well-circumscribed nodules ranging in size from few millimeters to several centimeters in diameter.[1] These tumors are composed of well-differentiated proliferative smooth muscle cells that form intersecting fascicles, without atypia, necrosis or mitotic figures. The figure shows a pulmonary nodule (a - H&E staining) and immunohistochemical staining. The nodule is positive for SMA (Anti-Smooth Muscle Antibody — b). The cells show positive immunoreactivity toward desmin (figure e) and estrogen receptors (figure d) and have a negative imuunireactivity toward TTF1 (figure c) and CD34 (figure f).

also performed, which showed a disappearance of dominant nodules, only centrilobular micronodules remaining. Initial diagnosis was of hypersensitivity pneumonitis secondary to aviary exposure and conservative treatment with clinical and imagological surveillance was decided on.

After 9 months, an increase in the size of all the nodules was detected, some now with cavitation (Fig. 1 c). A transthoracic biopsy was therefore proposed, which revealed histologic findings consistent with a benign metastatic leiomyoma (Fig. 2). Subsequently, the patient underwent a total hysterectomy with bilateral adnexectomy, later confirming the diagnosis of uterine leiomyomas. Computer scan images requested 4 months after surgery revealed partial regression of the nodules. The patient remains under follow-up and the lesions were stable at last reevaluation, 2 years after surgery (Fig. 2 c and d).

Benign metastatic leiomyoma (BML) is a rare entity of unknown prevalence; a 2017 review reports 161 cases described in the literature between 1 January 1965 to 10 April 2016, only 10 in women who have not undergone prior surgery.[1] The first reported case described a patient who died due to extensive pulmonary metastasis later identified as leiomyomas present in the uterus.[2]

Benign metastatic leiomyoma usually affects women with a history of uterine leiomyomas, metastasizing to extrauterine sites. The most frequent sites of metastasis are the lung and lymph nodes, with the most common presentation being multiple pulmonary nodules composed of smooth muscle cells.[3] Benign metastatic leiomyomas have also been detected in the mediastinum, retroperitoneum, vascular channels, bone, heart, skeletal muscle, and soft tissues.[3]

The diagnosis usually occurs incidentally in a chest radiography, or postmortem. Clinical course is generally indolent and most patients are asymptomatic. However, some may present with cough, wheezing, dyspnea, or chest pain.[3,4]

The mean age at time of diagnosis is 47 years old.[1] BML is more frequent in women who have undergone previous myomectomies or hysterectomies, one of the theories being the possibility of peritoneal seeding at the time of surgery, with subsequent metastasis.[1] This theory is not consensual, because there are rare, reported cases in which women did not have a history of uterine interventions. The etiology of the disease remains unknown.

Imaging findings of BLM are nonspecific and overlap with other entities, making the diagnosis by imaging alone almost impossible. On thoracic CT, BML typically presents as multiple bilateral well-defined non-calcified solid nodules of variable size, without a predominant distribution pattern.[5] Unilateral or solitary nodules can occur but are less common. Other rarely described features include associated interstitial lung disease, a miliary pattern, cystic lesions, and cavitation.[6,7] Uptake on FDG-PET is usually weak or absent[7] and there is no associated pleural effusion or mediastinal lymphadenopathy.[5]

Treatment is not standardized due to the rarity of the disease. Lung tumors may revert after menopause and during or

after pregnancy, supporting a role for estrogen in BML pathophysiology.[3] Surveillance, oophorectomy or hormonal treatment with antiestrogenic therapy are options described in the literature. Lung lesions usually remain stable, with some cases of regression after treatment.

The presented case is relevant due to the rarity of the disease and the symptomatic presentation, in a patient with a recent diagnosis of a head and neck cancer and no history of previous myomectomies or hysterectomies. The differential diagnosis is broad and includes metastatic disease or a primary lung cancer, and both infectious and non-infectious causes of granulomas (tuberculosis, granulomatosis with polyangiitis, etc.). The recent bird exposure, and the reduction of size of the nodules during follow-up, added the possibility of a subacute hypersensitivity pneumonitis. In this case, the exposure to birds was detected after bronchoscopy, so bronchoalveolar lavage had not been performed. It was a challenging case and is an example of the importance of a multidisciplinary discussion. In high-risk patients for metastatic lung disease, it can be difficult to consider benign causes of multiple lung nodules. Nonetheless, radiologists must be familiarized with BML given that it is associated with a very specific demographic and can be easily included or excluded in a differential.[7] It's important to highlight the importance of a thorough clinical history and physical examination even in cases that may seem straightforward at first.

Ethical considerations

Written informed consent was obtained from the patient for publication of this article.

Conflicts of interest

The author has no conflicts of interest to declare.

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LETTER TO THE EDITOR

Coinfection of pulmonary nocardiosis and nontuberculous mycobacterial pulmonary disease in patients without known immunodeficiency

Dear Editor

Both pulmonary nocardiosis and nontuberculous mycobacterial pulmonary disease (NTM-PD) have been reported in immunocompromised or immunocompetent patients; however, few articles have reported their coinfection,[1—3] and most of them are in patients with immunodeficiency. Here, we present a case series of coinfection with pulmonary nocardiosis and NTM-PD in patients without known immunodeficiency, and describe the characteristics of this population.

From January 2017 to July 2021, NTM and *Nocardia* isolates were collected from respiratory tract samples, including the sputum, bronchial wash, bronchoalveolar lavage fluid (BALF), and lung biopsy specimens at our hospital. *Nocardia* was identified based on colony morphology and positive modified acid-fast staining. The species were further identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *Mycobacterium* was also identified by colony morphology and acid-fast staining. When the *M. tuberculosis* antigen test was negative, the species were further identified by universal 16s rRNA gene sequences to confirm the diagnosis of NTM. NTM-PD was diagnosed based on a combination of clinical, radiological, and microbiological features, as described by the American Thoracic Society Mycobacterial Disease Subcommittee.[4] Pulmonary nocardiosis was diagnosed when the patient had pulmonary symptoms, radiological abnormalities, and at least one positive culture from sputum, bronchial wash, BALF, or lung biopsy.

From 448 patients with NTM infection, *Nocardia* was isolated from 14. All 14 patients had pulmonary symptoms and radiographic opacities. According to the diagnosis definition, four patients were excluded because NTM was isolated from the sputum only once. Therefore, coinfection of pulmonary nocardiosis and NTM-PD were identified in 10 patients. All these patients were absent from active malignancy, human immunodeficiency virus infection, corticosteroid or immunosuppressive drug use, solid organ transplantation, or stem cell transplantation. The clinical data of these patients are summarised in Table 1.

The mean patient age was 59.2 ± 11.7 (range 45-84) years, with an apparent female predominance (female:male ratio 4:1). Bronchiectasis was noted in all patients, with chronic obstructive pulmonary disease (COPD) observed in 5/10 patients. Two patients had a history of smoking and one, alcohol abuse. No patient had diabetes mellitus or pulmonary tuberculosis.

All patients had NTM-PD first, with pulmonary nocardiosis diagnosed simultaneously or 2—20 months after NTM-PD. At the time of diagnosis of pulmonary nocardiosis, all patients exhibited cough and sputum production, followed by dyspnoea in 7/10 patients, haemoptysis in 6/10 patients, and fever in 3/10 patients. Both NTM and nocardiosis in all patients were confined to the lungs, without dissemination. The leading species were *Mycobacterium intracellular* in NTM-PD and *Nocardia otitidiscaviarum* and *Nocardia cyriacigeorgica* in pulmonary nocardiosis.

Chest computed tomography (CT) revealed diffuse bronchiectasis and opacities in all patients, along with nodules, masses, infiltrates, and consolidations. The nodules were centrilobular, and all patients showed a diffuse tree-in-bud appearance. Cavities were noted in the upper lobes or superior segment of the lower lobes of three patients. One patient showed atelectasis. No patient had pleural effusion.

All patients were treated medically for at least one year, followed-up for 1—3 years, and were all alive in March 2022. Patients with NTM-PD were mainly treated with rifampicin, ethambutol, and clarithromycin/azithromycin. Patients with pulmonary nocardiosis were mainly treated with levofloxacin/moxifloxacin ± minocycline. Only one patient was treated with sulfamethoxazole (TMPCO). Post-treatment, seven patients improved clinically and radiologically, two maintained stable symptoms and chest CT findings, and one progressed slowly, with new lesions on chest CT. Sputum cultures during follow-up were negative in 4/4 patients with NTM-PD and 6/7 patients with pulmonary nocardiosis.

NTM-PD is strongly associated with bronchiectasis. Previous studies showed that the rate of NTM-PD in non-cystic fibrosis bronchiectasis was 5%-30%[5]; however, the causal relationship between the two diseases has not been fully established. The risk of pulmonary nocardiosis is increased in immunocompromised patients, particularly in those with defects in cell-mediated immunity. However, patients with chronic lung diseases, such as COPD and bronchiectasis, also have an increased risk of *Nocardia* infection. Lower airway bacterial colonisation in chronic lung diseases has been

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Table 1 Clinical data of 10 patients with coinfection of pulmonary nocardiosis and nontuberculous mycobacterium pulmonary disease.

No. (Sex)	Species of NTM	Species of *Nocardia*	Time interval from NTM to nocardiosis	Treatment	Outcome	Sputum cultures during follow-up
1 (M)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+LEVO	3 years, progress slowly	NTM, NA; *Nocardia*, positive
2 (F)	*M. intracellulare*	*N. cyriacigeorgica*	Simultaneous	RFP+EMB+AZI+MOXI	2.5 years, improved	NA
3 (F)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	MOXI+MINO	1 year, improved	NA
4 (M)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+MOXI+MINO	2.5 years, improved	Negative
5 (F)	*M. intracellulare*	*N. otitidiscaviarum*	Simultaneous	RFP+EMB+CLA+MOXI+MINO	2 years, improved	NA
6 (F)	*M. intracellulare*	*N. cyriacigeorgica*	Simultaneous	RFP+EMB+CLA+TMPCO	1 year, improved	Negative
7 (F)	*M. abscessus*	*N. farcinica*	2 months	CLA+LEVO	1 year, stable	NTM, NA; *Nocardia*, Negative
8 (F)	*M. intracellulare*	*N. farcinica*	4 months	RFP+EMB+AZI	3 years, stable	Negative
9 (F)	*M. intracellulare*	*N. cyriacigeorgica*	2 months	RFP+EMB+CLA+LEVO	2 years, improved	Negative
10 (F)	*M. intracellulare*	*N. beijingensis*	20 months	RFP+EMB+CLA+LEVO+MINO	3 years, improved	NA

NTM: nontuberculous mycobacterium; RFP: rifampin; EMB: ethambutol; CLA: clarithromycin; LEVO: levofloxacin; AZI: azithromycin; MOXI: moxifloxacin; MINO: minocycline; TMPCO: compound sulfamethoxazole tablet; NA: not available.

suggested to alter ciliary motility and cause epithelial damage, thereby facilitating the presence of *Nocardia*.[6] Therefore, bronchiectasis may be a connecting link between pulmonary nocardiosis and NTM-PD in immunocompetent patients. Interestingly, no patient in our series had extrapulmonary nocardiosis or NTM infection, which may be associated with underlying immunocompetence, to restrict infections within the epithelial-damaged lungs.

TMPCO has been the traditional antimicrobial of choice for pulmonary nocardiosis but was administered to only one patient in this study owing to a confirmed or suspected drug allergy in other patients. Quinolone ± minocycline was the treatment of choice for most patients in this study, with most patients showing favourable outcomes, compared with the high mortality rate of approximately 40% reported in the literature.[6] The favourable outcomes may be due to the immunocompetent nature of the patients and the confined infection within the lungs. Sulfamethoxazole-free regimens with other sensitive medicines for pulmonary nocardiosis appeared to be effective in this population.

Authors' contributions

SXF and SHL contributed to the conception of the study. SXF, LWJ and LLL contributed to data collection, data analysis and interpretation. SXF, LWJ and SHL drafted the manuscript. All authors revised the manuscript for intellectual content and approved the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval and consent to participate

The study was approved by the Research Ethics Commission of Peking Union Medical College Hospital in accordance with the Declaration of Helsinki. Informed consents have been obtained from patients or their relatives.

Availability of data and materials

All the data will be available to other researchers on reasonable requests to the corresponding author after publication.

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LETTER TO THE EDITOR

Azacytidine-induced pneumonitis in acute myeloid leukaemia

Dear Editor,

Myelodysplastic syndromes (MDS) represent a group of myeloid haematopoietic malignant disorders at hight risk of transformation into acute myeloid leukaemia (AML).[1] 5-azacytidine is a deoxyribonucleic acid (DNA) methyltransferase inhibitor and cytotoxic drug used since the year 2000 for the treatment of adult patients with AML, blast counts 20-30% and multilineage dysplasia.[2] The first application of this drug was in 1982, as a hypomethylating agent of the Y globin suppressor gene, to induce fetal haemoglobin in thalassemia.[2] The most common side effects of Azacytidine are: weakness, nausea, vomiting, constipation, injection site reactions and insomnia.[3] Although intersticial lung disease could be a classic complication of numerous therapeutics, it has been rarely described regarding 5-azacitidine.[2] Adverse drug reactions (ADR), particularly those that can be appreciably harmful and life-threatening, must be described to predict hazards in future applications, resulting in adjustments to the dosage regimen or in its definitive withdrawal. The Naranjo scale is the most used metric to determine an ADR[3] and its score can aid in identifying pulmonary toxicity. We also emphasise the importance of excluding the most common differential diagnosis, such as opportunist infections, diffuse alveolar haemorrhage (DAH), acute cardiogenic pulmonary oedema and leukaemic infiltration, detected in HRCT by the predilection of leukaemic cells involving the perilymphatic pulmonary interstitium[4]. After a literature review, we acknowledged this case as the 18th azacytidine-induced pneumonitis reported.

A 56-year-old male presented with pancytopenia, while admitted to the Pulmonology Department for the treatment of community acquired pneumonia complicated by pleural effusion. He was a former smoker (smoking load 40-unit-pack-year), had previous history of drug addiction (ended 15 years ago), namely cannabis, cocaine, and heroin, and a medical history of hypertension, type 2 diabetes, dyslipidaemia, insomnia, and major depression. He was chronically medicated with furosemide, glargine, atorvastatin/ezetimibe, sertraline, risperidone, and clonazepam. He underwent a thorough haematological evaluation that included medullar aspiration and a bone marrow biopsy. The results showed a MDS with progression to AML. Patient was discharged from the Pulmonology Department and admitted to the Ambulatory Haematological Service where he initiated treatment with 5-azacitidine at the conventional dosage of 75mg/m2 for 7 days.

On the 5th day of the second therapeutic cycle (C2D5), patient complained of sudden dyspnea, fever (38.1°C) and presented with rapidly progressive hypoxemia (highest necessary FiO2 was 0.60). The chest X-Ray performed showed bilateral parenchymal infiltrates and blood analyses revealed a moderate increase of inflammatory parameters. Patient was admitted at the Hematology Department. A sepsis screen was carried out, empiric antibiotics prescribed, and an angio-thoracic CT was performed to exclude pulmonary thromboembolism (PE). The scan did not show PE but revealed diffuse parenchymal ground-glass densification with an "NSIP-like" pattern (Fig. 1).

A pulmonology evaluation was requested. Suspected toxicity to azacytidine was suggested, once patient had a Naranjo score of 7 (probable ADR), and the drug was suspended. A complementary study was carried out. Bronchoalveolar

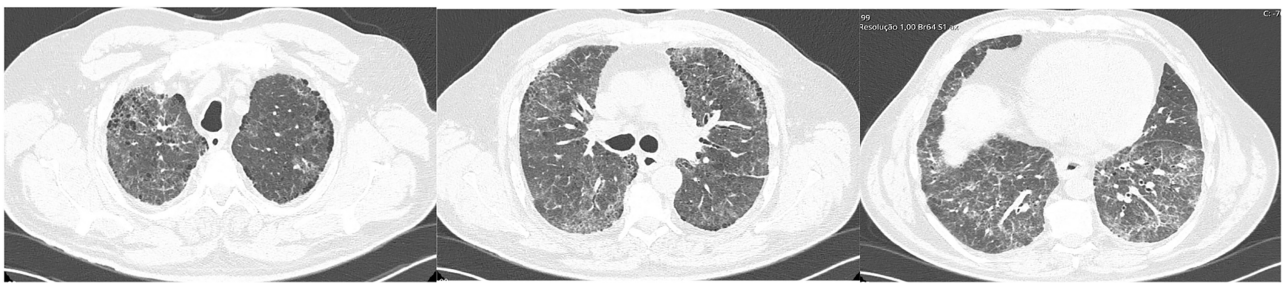

Figure 1 HRCT— diffuse ground-glass opacities with an "NSIP-like" pattern; presence of centrilobular and paraseptal emphysema.

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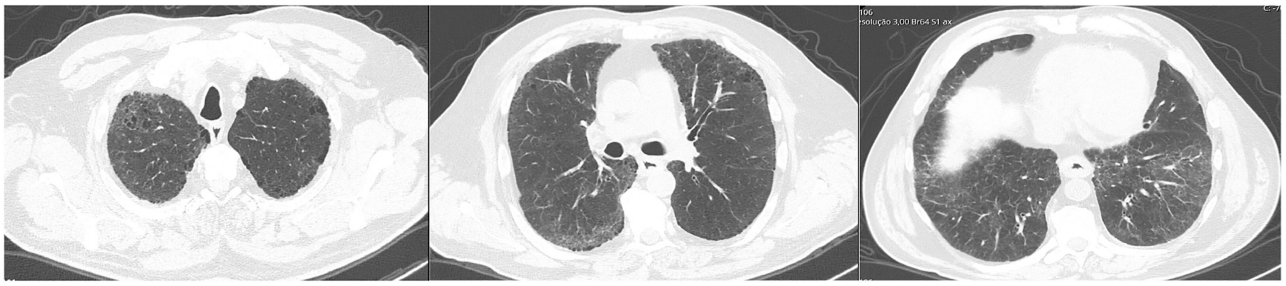

Figure 2 HRCT after 3 weeks of treatment — overall improvement of diffuse parenchymal ground-glass densification.

lavage (BAL) showed 320,000 cels/mL, 93% lymphocytosis and an extensive negative microbiological study, namely for *Pneumocystis jirovecii* and CMV, considering the high risk for opportunistic pulmonary infections in the haemato-oncological setting. Respiratory function tests revealed slight restriction (TLC 74%) and severe decrease in single-breath carbon monoxide diffusing capacity of the lungs (DLCOSB 35% and KCO 61%). Despite the absence of elusive clinical features (no orthopnea, paroxysmal nocturnal dyspnea, crackles or peripheral oedema) and the NT-proBNP and HRCT pattern not suggesting cardiogenic pulmonary oedema, a heart evaluation is generally valuable and, therefore, an initial EKG and a subsequent echocardiogram were conducted and were both normal. The patient was prescribed 3 pulses of methylprednisolone 500 mg, followed by prednisolone 0.75 mg/kg in a slow tapering scheme, under PCP prophylaxis with trimethoprim/sulfamethoxazole. After 10 days there was clinical, gasometrical, and radiological improvement, having been discharged with ambulatory oxygen. After 3 weeks of treatment, a reassessment HRCT revealed a clear improvement, showing bilateral reduction of the ground-glass opacities (Fig. 2), and the 6MWT performed allowed the suspension of the previously prescribed oxygen.

In summary, azacytidine-induced pneumonitis is a diagnosis of exclusion and should be addressed after all relevant alternative diagnosis have been ruled out. This case confirmed an ILD secondary to toxicity to azacytidine due to the temporal link with the onset of the same, clinical-radiological agreement with previously described cases[3], and the exclusion of differential diagnoses such as opportunistic infection, DAH, acute cardiogenic oedema (no clinical features or positive biomarkers for heart failure) or leukaemic infiltration (HRCT negative for suggestive features such as thickening of interlobular septa and bronchovascular bundles[4]). The expressive BAL lymphocytosis, suggesting an immune-mediated mechanism, and the clinical and radiological improvement after drug suspension and corticosteroid therapy institution, were also decisive supporting elements.

In the appropriate clinical setting, this case report evokes the importance of a careful consideration towards the possibility of lung toxicity following hemato-oncological therapies, avoiding an unnecessary delay in drug suspension and the misuse of antibiotics.

Conflicts of interest

The authors has no conflicts of interest to declare.

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LETTER TO THE EDITOR

Recurrent pneumonia and severe opportunistic infections in declining immunity and autoimmune manifestations

To the Editor

We herein describe a 29-year old female referred to our attention due to adult onset bronchiectasis and hypogammaglobulinemia. Since early infancy, she had a history of Chronic Mucocutaneous Candidiasis (CMC), followed by a diagnosis of selective immunoglobulin IgA deficiency (Fig. 1). Two years later she developed type 1 diabetes (T1D) with good metabolic control on basal-bolus insulin regimen. Type 1 autoimmune polyendocrinopathy and chronic granulomatous disease were suspected and ruled out (i.e. normal autoimmune regulator-AIRE gene expression and nitroblue tetrazolium test, respectively). She later experienced recurrent inguinal and axilla abscesses. Immunological tests were thus expanded and revealed the onset of persistent B cells lymphopenia (Fig. 1) with poor lymphocytes proliferation in response to mitogens. Isohemagglutinins and response to vaccines were normal, whereas bone marrow biopsy showed a mild dysplasia. At the age of 21-years she developed pneumonia with severe sepsis, and empirical antimicrobial therapy was started with improvement. However, chest computed tomography (CT) scan performed at 3-month follow-up showed thickened walled cavitary lesions on the right upper lobe, bilateral bronchiectasis and bronchiolitis in the upper lobes. Based on the clinical history and immune profile, common variable immunodeficiency (CVID) was diagnosed, and subcutaneous immunoglobulin (Ig) replacement therapy and co-trimoxazole prophylaxis were initiated. Despite initial favourable response, she later continued to experience intermittent cough, shortness of breath and recurrent pneumonia. At the age of 28 she was diagnosed with Pneumocystis Jiroveci and Cytomegalovirus pneumonia, documented by microscopic examination of transbronchial lung biopsy specimens and broncho-alveolar lavage fluid (BALF) PCR, respectively (Fig. 2).

The patient was, thus, referred to our Unit. Immunological investigations were hence repeated and confirmed persisting B-cell lymphopenia with normal Regulatory T cells. Given the clinical history, Signal Transducer and Activator of Transcription 1 (STAT1) disorder was suspected and confirmed by targeted DNA sequencing. Namely, genetic analysis identified a rare de novo heterozygous STAT1 gene mutation (c.520T>C, p.Cys174Arg), previously reported as a pathogenic gain of function (GOF) mutation.

STAT1 plays a key role in orchestrating several pathways implicated in fundamental cellular processes, including interferons α/β signaling pathway.[1] STAT1 GOF mutations lead to complex disorders characterized by great variability in the clinical manifestations. Genetic-epigenetic factors may play a role in terms of clinical expression or onset timing, and prompt diagnosis may be missed.

In the largest cohort describing 274 patients with heterozygous GOF mutations,[2] the most common clinical feature was represented by fungal infections with CMC being the main manifestation at onset. Autoimmune diseases were also documented (43%), including T1D in 9%.[2] The incidence of aneurysms as well as malignances affecting the skin, larynx, and gastrointestinal tract (upper and lower) was higher compared to standard population.[2-4] Low Respiratory Infections were reported in almost 50%, mainly bronchitis or interstitial pneumonia. Whether or not bronchiectasis herein described is directly due to STAT1 signalling aberrance is not clear. Actually the progressive worsening of the combined immunodeficiency observed in our patient may be identified as putative factor causing the occurrence of newly acquired infections. Indeed, bronchiectasis is the ultimate outcome of many conditions due to recurrent respiratory infections.

A recent systematic review of 442 cases of STAT1 GOF mutations reported a higher risk of bronchiectasis in patients carrying the T385M mutation. However, our patients carried other type of mutation highlighting the need for proper microbiologic treatment in all patients with STAT1 GOF mutations.[4]

The humoral immunodeficiency herein reported was observed as a rare immunological abnormality in patients with STAT1 GOF mutations. Low B Lymphocytes or accelerated apoptosis in peripheral mature B-cells were described but the pathogenesis of impaired B cells response are still elusive.[3,5]

Abbreviations: STAT1, Signal Transducer and Activator of Transcription 1; GOF, Gain-of-Function; T1D, Type 1 Diabetes; CT, Computed tomography.

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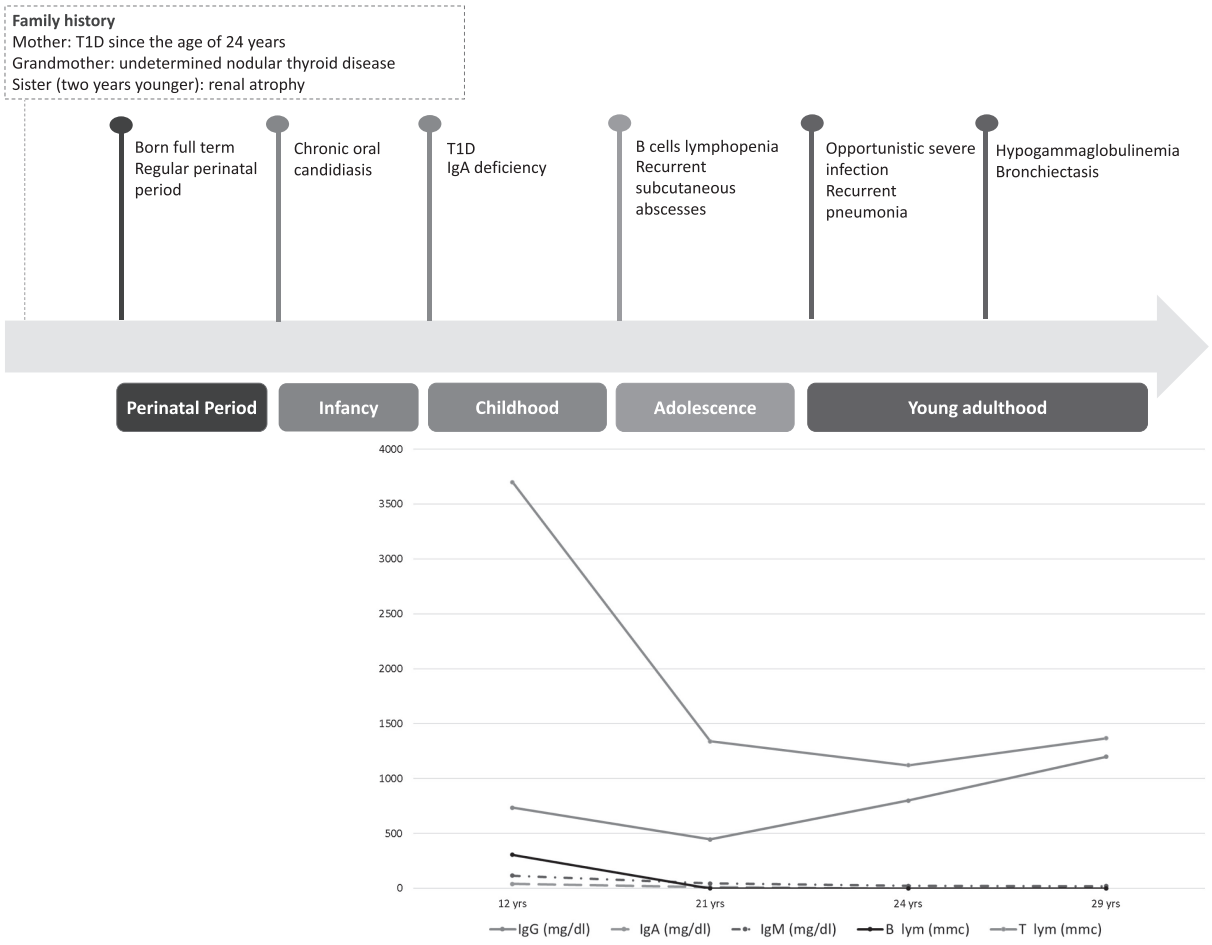

Fig. 1 Changes of serum immunoglobulin levels and blood T - B lymphocytes by age (SCIg = Subcutaneous Immunoglobulin; NBT= Nitroblue tetrazolium test; Abt= antibiotic) and timeline summarizing major events of the case.

The uniqueness of the case here described resides in the challenging diagnosis due to additional clinical insights occurring over time, eventually delineating a more comprehensive phenotype culminating only in adulthood (Fig. 1). Although rare, the association of bronchiectasis in a patient displaying humoral immunodeficiency, opportunistic infections and autoimmune diseases, should prompt physicians to investigate and underlying STAT1 signalling disorder.

Indeed, early diagnosis may allow a dedicated multidisciplinary approach in order to reduce morbidity and mortality. Hematopoietic stem cell transplantation has been performed in few patients and with inconsistent results and high mortality[6] and current treatment regimens are mainly supportive. However, recent novel treatment strategies targeting type I interferon signalling by systemic administration of JAK1 and JAK2 inhibitors have been successfully used in some patients.[7] Regarding our patient, once the diagnosis was finalized, we referred her back to adult specialists in order to attempt the newly identified JAK1/2 inhibition therapeutical strategy.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report.

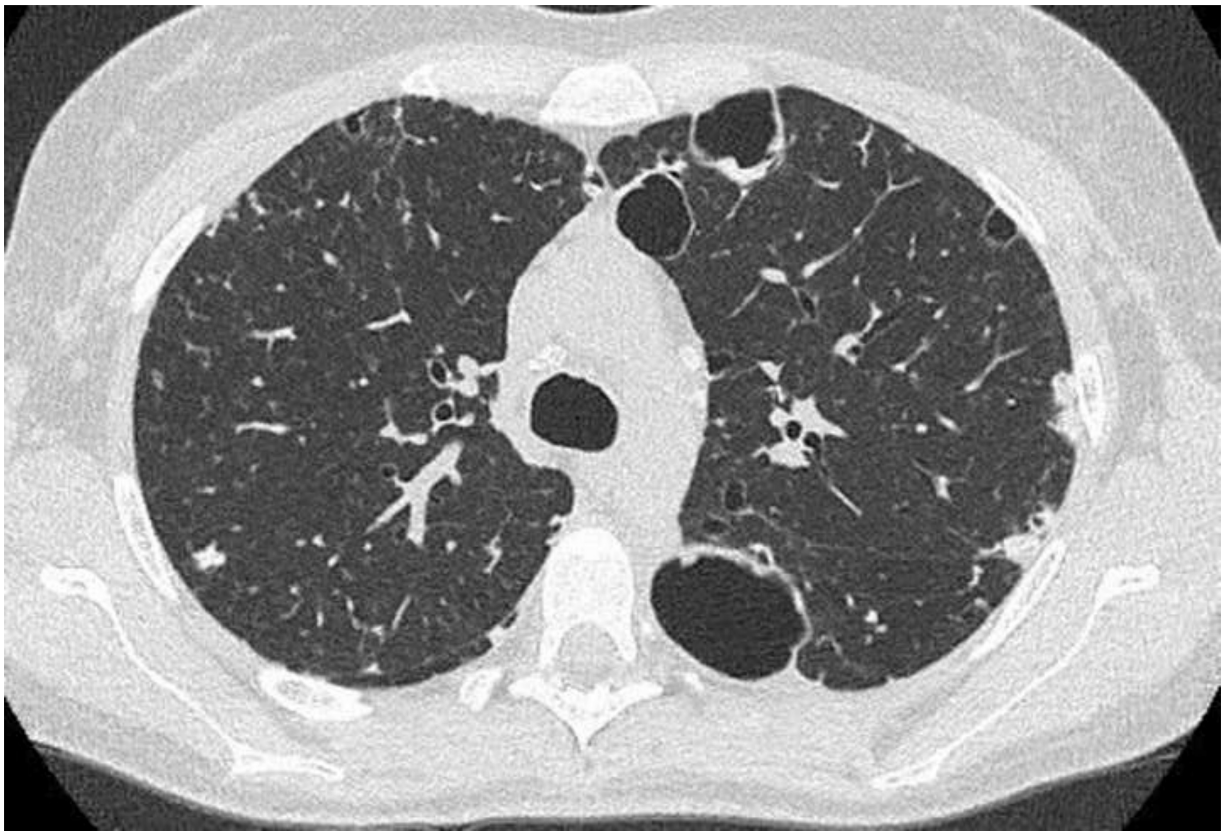

Fig. 2 CT scan findings. Cysts with thickened walls in subpleural regions (the biggest are in the left lung); subpleural bilateral focal consolidation centrally cavitated. Centrilobular nodules are present in the anterior segment of the right upper lobe as well. Transbronchial lung cryo biopsies documented Pneumocystis jirovecii infection.

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LETTER TO THE EDITOR

A curious manifestation of mechanical tension theory in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown cause that primarily occurs in older adults.[1,2] It is characterised by the histopathologic and/or imaging pattern of usual interstitial pneumonia (UIP), typically with peripheric involvement and a cranio-caudal gradient.[1,2]

The reason for the peripherical predominance, which generally starts at the posterior bases of the lower lobes and then progressively extends in a caudal-cranial mode, remains unknown.[1-3] One hypothesis suggests that the concurrent action of cell senescence, genetic predisposition, exposure to cigarette smoke and mechanical stress caused by respiratory lung movements leads to the localised exhaustion of the tissue renewal capacity and, eventually, alveolar loss and abnormal lung remodelling.[3-5]

We present the case of a patient who developed a probable UIP pattern after undergoing a left lower lobe (LLL) lobectomy due to a tumour. Interestingly, the patient's remaining left upper lobe (LUL) exhibited reticulation and traction bronchiectasis that resembled the features usually observed in the lower lobes, which indicated the possible relevance of mechanical tension theory. The patient consented to the publication of this clinical case.

A 70-year-old male former smoker underwent a computed tomography (CT) scan that revealed a 13-mm LLL cavitated nodule (Fig. 1A), which the CT transthoracic biopsy indicated to have features of squamous cell lung carcinoma. After staging, the patient underwent an LLL lobectomy with lymph node removal. The pathologic assessment revealed a stage I tumour (pT1b N0 R0) according to the American Joint Committee on Cancer criteria (7th edition). No other histologic features related to interstitial lung disease were identified. The patient was admitted for follow-up and no adjuvant therapy was administered.

During follow-up, the patient remained stable, with his only respiratory symptom being exertional dyspnoea (Modified Medical Research Council Dyspnoea Scale score = 1). However, the protocolled 18-month CT scan revealed a peripheral and basal reticulation with traction bronchiectasis, which persisted at the 21-month assessment and exhibited slight progression at the 24-month evaluation. Although bilateral, these imaging features were more evident in the inferior portion of the LUL (Fig. 1B).

After a multidisciplinary team (MDT) discussion, a cryobiopsy of the patient's LUL was performed, which revealed the replacement of portions of alveoli by irregular fibrous scars in a patchwork pattern and fibroblast foci. The scars were composed of collagen with scant chronic inflammation. Moreover, their distribution was predominantly paraseptal. The adjacent pulmonary parenchyma presented minimal interstitial inflammation. These aspects were compatible with a UIP pattern (Fig. 2).

Apart from being a former smoker, the patient did not report any relevant exposures and his autoimmune panel was within the normal range. The final diagnosis of IPF was established during an MDT meeting and the patient was prescribed 801 mg of pirfenidone three times a day.

Following an LLL lobectomy, the development of an UIP pattern mainly affecting the LUL strengthens the potential relevance of mechanical tension in relation to the manifestation of fibrosis. Pre-existing factors such as ageing, exposure to environmental pollutants (e.g. smoking habits) and unknown genetic abnormalities may promote the occurrence of IPF after an insult that increases the magnitude of the respiratory mechanical stress.[3,4] Mechanical forces can be particularly concentrated in the peripheral and basal anatomical parts of the lung, thereby triggering the formation of microscopic damage to the alveolar structure, which may cause repetitive small scarring events (fibroblast foci) and, eventually, honeycomb changes.[4,5] Additionally, a subsequent increase in the extracellular matrix stiffness and the progressive scarring of the lung tissue significantly change the respiratory mechanics, rendering the lung more fragile and more exposed to non-physiological stress during both spontaneous breathing and mechanical ventilation, which can promote progressive lung damage and the dysregulation of mechano-transduction and tissue repair.[4,5]

Carloni et al. demonstrated that mechanical stress during lung inflation is heterogeneously distributed in different anatomical parts of the lung parenchyma and, further, that these overloaded regions correspond to those involved in early IPF lesions.[5] More recently, Wu et al. showed that the loss of Cdc42 function in alveolar stem 2 cells (AT2) causes periphery-to-centre progressive fibrosis.[6] It has been established that the application of mechanical stretch to AT2 cells activates the transforming growth factor beta (TGF-β) pathway, which induces a disturbance in the homeostatic

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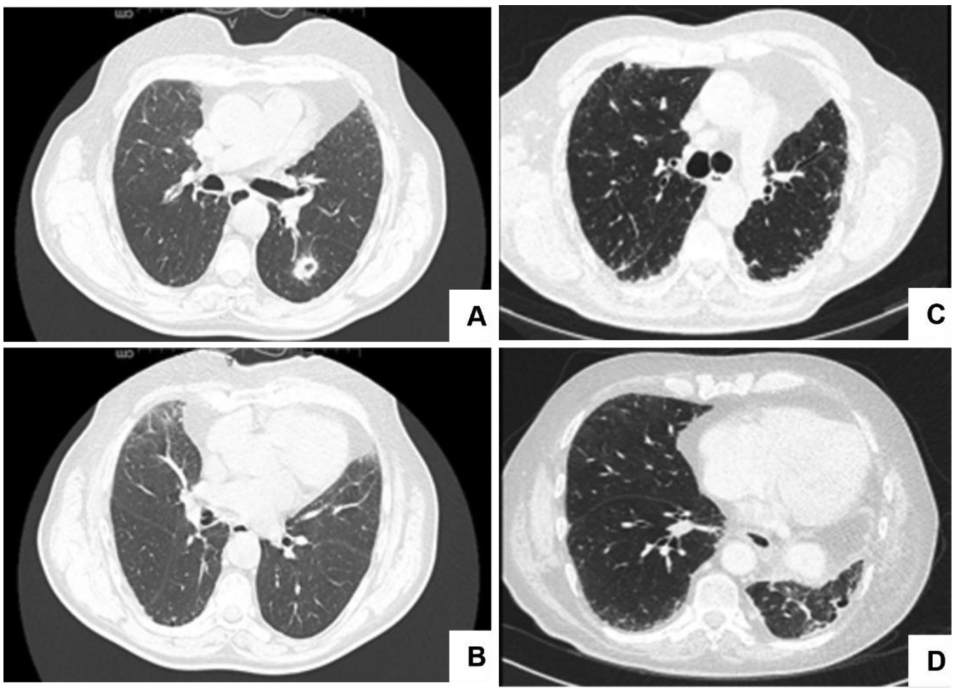

Fig. 1 CT scans before and after left lower lobe lobectomy (LLL). Fig. 1A shows a 13 mm cavitated nodule in the LLL, posteriorly confirmed to correspond to a squamous cell lung carcinoma; no signs of interstitial lung disease were present in the lower lobes (Fig. 1B). Fig. 1C and D shows bilateral peripheric and basal reticulation and traction bronchiectasis in the inferior region, more evident in the left upper lobe, 21 months after LLL lobectomy.

microenvironment, leading to aberrant wound healing and promoting the fibrotic process.[6,7] The authors also showed that Cdc42-null AT2 cells in post-pneumonectomy and untreated aged mice could not regenerate new alveoli, resulting in sustained exposure to elevated mechanical tension, which activated TGF-β signalling.[6] This study provides new insights that emphasise the association between mechanical tension and progressive lung fibrosis.[6]

The precise recognition of this physiologic process is vital, as it can inform the identification of preventive measures to avoid fibrosis and suggest new therapeutic paths.

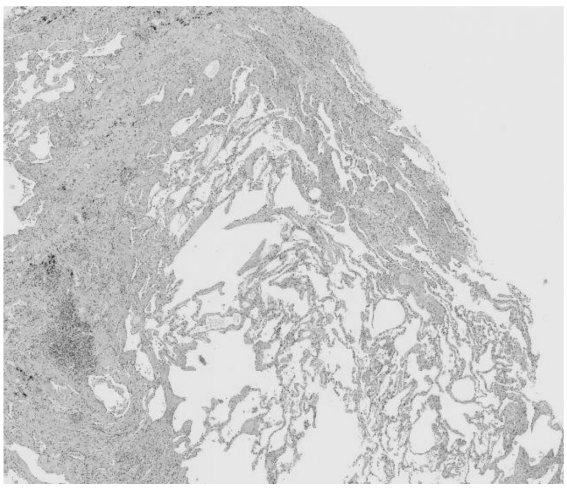

Fig. 2 Histology of the cryobiopsy performed in the left upper lobe. At this magnification, normal alveolar tissue is surrounded by portions of alveoli replaced by irregular fibrous collagenous scars, with a predominantly paraseptal distribution. At higher magnifications, fibroblast foci were seen. The adjacent parenchyma has minimal interstitial inflammation. The aspects were compatible with usual interstitial pneumonia.

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.06.008.

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LETTER TO THE EDITOR

‘Gold-standard’ field test is a non-sequitur

We read with interest the letter by Combret and colleagues[1] describing the 6-min walk test (6MWT) as the ‘gold standard’ field test for the evaluation of exercise capacity. The study population described by Combret’s group is of young people with cystic fibrosis (CF) with mean age 12 years, and near-normal lung function (mean FEV_1 95.8% predicted). It would be our opinion that a 6MWT would be of limited utility in evaluating exercise capacity in a group of healthy children with CF — it is a non-externally paced, non-incremental, volitional test that is sub-maximal for all barring those with advanced lung disease.

Indeed, mean (SD) end-exercise heart rate (HR) was 126 (24) beats.min^{-1} in the children studied suggesting (very) low cardiorespiratory stress. Whilst we acknowledge the utility of the 6 MWT in people with CF undergoing transplant assessment and those with very low lung function, we would see no evidence to support the notion of the 6MWT being useful in the cohort described. Furthermore, the peak HR reported on 1-min sit-to-stand (1-min STS) testing [mean (SD) 116 (20) beats.min^{-1}] would lead us to question the motivation (internal and external) of the individuals tested. This is significantly lower than the achievement of an average HR of approximately 90% of the maximum HR measured during an exhaustive cycle cardiopulmonary exercise test on the 1-min STS that has been reported previously by other groups.[2,3]

We acknowledge that cardiopulmonary exercise testing with breath by breath gas analysis is not universally available. The next best test recommended in a joint statement endorsed by the European Respiratory Society and the European Cystic Fibrosis Society Exercise Working Group would be to perform a maximal workload test on a cycle ergometer with continuous measures of HR and oxygen saturation.[4] Such a test would be expected to achieve a near-maximal HR and detect any exercise related desaturation. There are some tests e.g. 25-level modified shuttle test (MST-25)[5] which are incremental, externally-paced, and do have the potential to measure maximal exercise in people with CF; these tests in our opinion would be better field tests than 6 MWT.

Perhaps most importantly no field test can be defined as ‘gold standard’ due to the lack of precision in understanding whether exercise limitation is physiological or volitional.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Validity and reliability of the one-minute sit-to-stand test for the measurement of cardio-respiratory responses in children with cystic fibrosis. Authors' reply

We would like to thank Dr. Urquhart and colleagues for their correspondence on our work reporting the cardio-respiratory responses observed during the 6 min walking test (6MWT) and the one-minute sit-to-stand test (STST1') in children with cystic fibrosis (CF).[1,2] Their comment opens up a discussion that is critical for the CF community, and that goes beyond the objectives of this work. The rationale for choosing the 6MWT as a reference test was simplified in our research letter, but this commentary will allow us to elaborate on this choice.

It is undeniable that the 6MWT cannot be considered as the *'gold standard'* for all the children with CF. Dr. Urquhart and colleagues underscored its limits: the 6MWT is self-paced, non-incremental, and submaximal for the majority of CF children. However, we chose the 6MWT as the reference test in this work because it is the most widely used field test for these people, even in pediatric centres. Calling the 6MWT a *'gold standard'* might be imprecise, but recent surveys witness that it is still widely regarded as the reference field test in the CF clinical practice landscape.[3,4] We have therefore chosen to use the 6MWT to enhance the applicability of our results. Furthermore, we reported the association between the cardio-respiratory response during both tests, and discussed the possibility of using the STST1' as a surrogate to the 6MWT. It was not our aim to establish that either of these tests was a reference.

Peak heart rate (HR) reached during both tests in our cohort was very low. Reaching a high level of motivation to perform the STST1' and the 6MWT for young people with CF (pwCF) is challenging. The unpleasantness of both tests can lead to demotivation, especially as our protocol required two rounds of each test to evaluate reliability. The time perception was also probably different in our cohort of young pwCF, compared to other cohorts of adults.[5] Finally, our study was descriptive meaning that the investigations took place during a standard medical consultation, or at the time of the annual review. Contrarily, other studies showing a higher level of exertion with the STST1' included adult pwCF undergoing a pulmonary rehabilitation program, and who, in turn, were probably highly motivated to achieve the best possible performance.[6,7]

To conclude, we acknowledge the core message of this comment. Exercise testing for young pwCF should present sufficient cardio-respiratory challenge. Simple submaximal field tests (e.g., the 6MWT or the STST1') may not be difficult enough to expose exercise-related symptoms, and a ceiling effect would be observed in children with near-normal lung function. However, there are still important discrepancies between the procedures described by the European Cystic Fibrosis Society Exercise Working Group, and the current practices in the CF centers. It is an important challenge for the future that these approaches become commonplace within clinical practice worldwide, especially since the physical fitness of young pwCF is expected to improve in the CF transmembrane conductance regulator (CFTR) modulators era, which will further reduce the usefulness of submaximal exercise tests.

Declaration of Competing Interest

Dr. Combret, Dr. Prieur and Dr. Medrinal report performing expertise activities for Air Liquide Medical Systems, outside of the submitted work.

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PHOTO

Complete bronchial rupture due to blunt chest trauma

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We present the clinical case of a 24-year-old patient diagnosed by computed tomography (CT) of an injury to the left bronchial tree following evidence at this level of reduction in caliber and loss of mural definition (Fig. 1A) after suffering a blunt chest trauma.

A diagnostic bronchoscopy was performed which confirmed loss of substance and complete amputation of the left main bronchus (Fig. 1B). At the same time, selective contralateral intubation guided by bronchoscopy was performed. The patient underwent emergency surgery by left anterolateral thoracotomy, revealing complete bronchial destruction, which made anastomosis impossible. Extrapericardial left pneumonectomy was performed (Fig. 1C). The patient underwent a complicated postoperative stage leading to a control CT scan which revealed pseudoaneurysm of the thoracic aorta; this was surgically excluded by endovascular placement of a prothesis (Fig. 1D). The patient presented slow improvement in respiratory function parameters, allowing discharge 64 days after hospital admission. After 2 years of follow-up, the patient has not presented any postoperative complications or hospital readmission.

The clinical picture of a patient with a bronchial rupture may initially be nonspecific, but there should be a high index of diagnostic suspicion in the presence of respiratory failure, subcutaneous emphysema, pneumomediastinum, pneumothorax with persistent air leak and/or failed lung reexpansion despite placement of a pleural drain.[1]

Once the condition is recognized, selective intubation, guided by fiberoptic bronchoscopy, of the bronchial tree contralateral to the lesion is recommended. Surgery should be immediate if the initial measures do not resolve a life-threatening condition. Surgical treatment of bronchial rupture is the early reestablishment of the anatomical continuity of the tracheobronchial tree by means of surgical repair of the lesion when possible,[2] reserving pneumonectomy for those cases in which the bronchial tree cannot be reconstructed, as in the case described.

In conclusion, bronchial ruptures are infrequent entities with high mortality that occur mainly in polytraumatized patients, frequently associated with other serious concomitant injuries that can appear both initially and later.[3]

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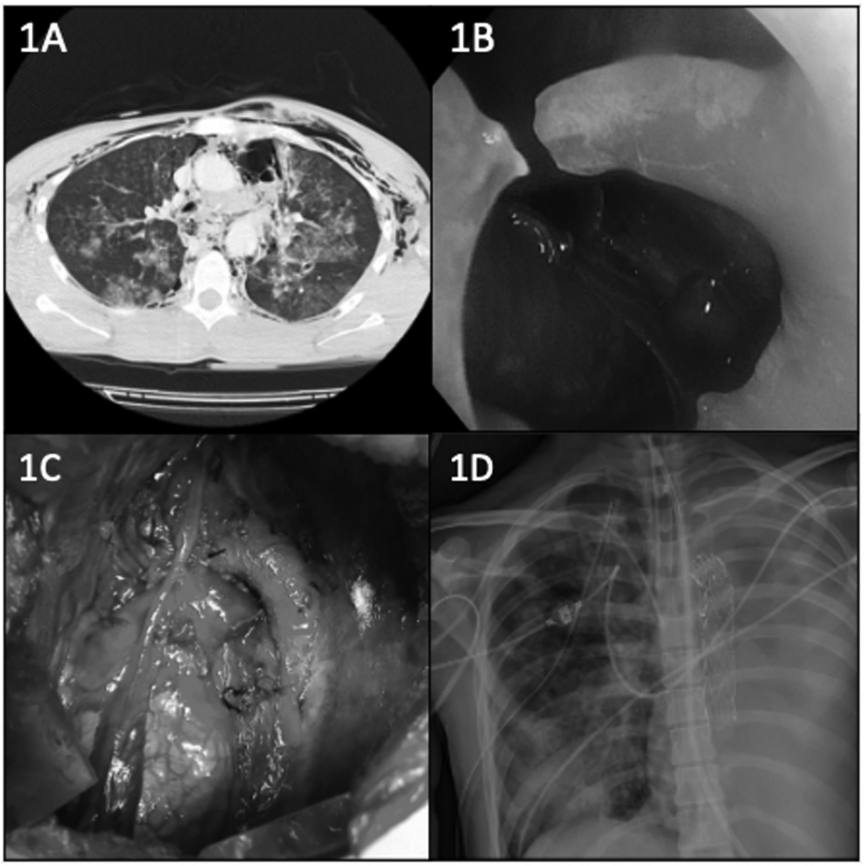

Fig. 1 (A) Chest CT image: Subcutaneous emphysema. Pneumomediastinum. Diffuse bilateral pulmonary contusion. Reduction in caliber and loss of mural definition of the left main bronchus. (B) Endoscopic image: Complete amputation of the LMB with visualization of the left pleural cavity through it. (C) Intraoperative image: Extrapericardial left pneumonectomy after ligation of the ductus arteriosus and preservation of the phrenic nerve. (D) Postoperative chest X-ray. Valiant-type prosthesis is observed in the thoracic aorta distal to the left subclavian artery.

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