SUGGESTIONS FOR LUNG FUNCTION TESTING IN THE CONTEXT OF COVID-19

BY:

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ABSTRACT

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[2] ASL – *Azienda Sanitaria Locale-Ospedale/unità operativa igiene e sanità pubblic*a - Local Health

Authority/Public Health Care Service, but may also more specifically refer to The Department of Environmental Health (in Britain) which is a government department dealing with all aspects related to public health and hygiene - food hygiene and safety, safety at work, pest control et

[3] UOC (*Unità Operativa Complessa*) – Multispecialty Department

[4] IRCCS (*Istituto di Ricovero e Cura a carattere scientifico*) – Hospital for excellence in clinical research and

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[5] AOU (*Azienda Ospedaliera Universitaria*) - University Hospital Trust

[6] ASST (*Aziende Socio Sanitarie Territoriali*) - Local Health Authority/Public Health Care Service, but may also

more specifically refer to The Department of Environmental Health (in Britain) which is a government department dealing with all aspects related to public health and hygiene - food hygiene and safety, safety at work, pest control etc

[7] Fondazione IRCCS (*Istituti di Ricovero e Cura a Carattere Scientifico*) = Scientific Institute for Research,

Hospitalization and Health Care

[8] AUSL – *Azienda Unità Sanitaria Locale* – Local Area Health Authority Unit

[9] SOS (*struttura operative semplice*) – Department, Division, or Unit in a hospital

[10] ASP (*Azienda di Sanità Pubblica*) – Local/Provincial Public Health Care Authority

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The coronavirus disease 2019 (COVID-19) pandemic is currently a challenge worldwide. The role of lung function testing is well defined for the diagnosis of various diseases and conditions. They are also indispensable in the

evaluation of the response to medical treatment, in the follow up of patients' respiratory and systemic pathologies and in the evaluation of preoperative risk in cardiothoracic and major abdominal surgery. The opportunities for transmission of COVID-19 remain partially unknown and the data is continuously evolving. Lung function testing represent a potential way for COVID-19 transmission due to aerosol generation during any procedure and concentration of patients with pulmonary disease in lung function laboratories. This document provides some useful information on the risks and relative recommendations that vary according to the phase of the pandemic. It may support national and regional boards and the health authorities to which they belong. There is a need of a rapid reopening
of lung function laboratories but maximum safety is required in the COVID-19 era.

INTRODUCTION

In accordance with a recent document from the American Thoracic Society (ATS) [1] and another from the European Respiratory Society-ERS [2], lung function testing represent a potential way for COVID-19 to be transmitted because of the concentration of patients with pulmonary disease in lung function laboratories and because of the potential generation of aerosols during any procedure. Moreover it is impossible to wear surgical masks during spirometry operating procedures, due to the duration of patient contact with the operator (>15 minutes). This is a common problem for otolaryngologists, specialists, and dentists who present similarities due to type of exposure [3]. Although most patients are subject to screening for symptoms prior to admission to health care units, patients with respiratory diseases may exhibit symptoms comparable with COVID-19 infection.

Opportunities for transmission remain unknown and the data is continuously evolving. The risk varies according to the prevalence of the virus in the community, age, seriousness of the pulmonary disease, and immunosuppression. Consequently, the recommendations made in the ERS document [2] are useful. They vary according to the phase of the pandemic. In the phase 1 they provide for total suspension of lung function testing practically limited to preoperative evaluation only. Always with maximum safety in mind, services are allowed to restart in the "post-peak" phase. The activity may only proceed according to “standard” precautions when the viral presence is low and rapid and reliable methods are quickly available to evaluate contagiousness based on a combination of symptoms screening and diagnostic tests.

The role of lung function testing is well defined for the diagnosis of various diseases and conditions such as asthma, chronic obstructive pulmonary disease (COPD), chronic respiratory failure (CRF), sleep related breathing disorders (SRBD), or it is better to evaluate their clinical picture such as in patients suffering from interstitial lung disease (ILD). The lung function testing are also indispensable in evaluating the response to medical treatment, in following up patients with pulmonary or systemic pathologies with pulmonary involvement as well as in evaluating preoperative risk in thoracic and abdominal surgery with a view to the patient being added to the transplant list. In particular, functional evaluation of COPD is desirable because early diagnosis of a disease identified late incurs high socio-health costs.

It has also been noted for some time that lung function laboratories have several sources of more or less high risk of cross-infection between patients and operators. Numerous works and ERS/ATS workshop reports have been published in the literature since the 1990s that have provided very accurate information for the prevention and control of viral/bacterial infections [4-6]. Then the official ATS/ERS document on the standardisation of respiratory functionality examinations was published in 2005 whose chapter “Hygiene and infection control” [7], updated in 2019 [8], still represents the official guideline today. Since then it has been imperative for all laboratories to have an infection control policy that includes all aspects concerning the methods of washing, sterilisation, use of protective equipment, and specific training of personnel. To emphasise the need for constant control of the infection, other indepth

research works and updates have been published in recent years that have focussed on this problem [9-10]. The current COVID-19 epidemic and the need to re-open the lung function laboratories have led to a dramatically revision, in particular of the documents available until now, and then to a rethinking of these measures in the context of COVID-19, by taking into account the individual characteristics of the traditional lung function laboratory and the equally unique characteristics of the virus and still not fully understood [11-12].

The recent ATS document [1] has emphasised the intrinsic risk in spirometric manoeuvres capable of generating aerosol. At the time of writing, there is only one international confirmation of the management of patients with allergy and immunological diseases [13] that reaffirms the risk from spirometric manoeuvres, also underlined in a Global Initiative on Asthma (GINA) document [14] which has suggestions for limiting the diffusion of the virus in ambulatory environments, useful for the purposes of this paper. Another theme to be confronted is the sanitization of instrumentation required to for nocturnal cardiorespiratory monitoring in the light of the COVID-19 pandemic. The confusion over the management of patients with Obstructive Sleep Apnoea Syndrome (OSAS) who needs respiratory

support to be activated (with Continuous or Bi-Level Positive Air Pressure), that is, by its calibration/adaptation in clinical practice (15), which needs to be subject to in-depth study

This document aims to provide several specific indications in the new context caused by COVID-19, on the control of infection in carrying out the main lung function testing in addition to what has already been codified for all of the infections in the 2005 official document [7], updated in 2019 [8]. All of this has become indispensable for all patients who have the appropriate indication in view of the re-opening of lung function laboratories in the so-called phase 2 (post-peak). In particular, it is also extremely important that these indications are considered in view of the opening of new follow up studies dedicated to "post-COVID" patients in which examinations of lung function testing are included in evaluating any residual functional damage.

This document is focused on the need to identify patients with indications for spirometry in phase 2, having moreover taken all possible reasonable actions to exclude an active infection according to protocols decided by the individual medical facilities and departments (e.g. 24-48 hour telephone contact before the appointment, triage immediately before entering the medical practice).

GENERAL WARNINGS

Medical practices must be accessed through well-defined entrances that the users can reach easily (also signposted) in order to guarantee controlled flows and reduce the time the patients spends inside the practice to a minimum. In addition to the time required to carry out the lung function testing, it is also necessary to calculate air exchange and renewal for approximately 15 minutes in accordance with the ERS document.

SPECIFIC WARNINGS

In addition to all that is generally provided by medical protocols for access to health facilities, the following procedures are recommended:

a) Pre-triage telephone contact to avoid a manifestly suspect patient accessing the waiting room, the call to be made as close as possible to the date of the service (24-48 hours before) [see appendix];

b) nasopharyngeal swap samples for suspect patients in the 48-72 hours before the respiratory functional exam;

c) reception of the patient respecting social distancing indications (legal regulations) with taking of body temperature and targeted anamnesis;

d) only patients (and any companions) with a surgical mask (or equivalent mask with filtration certificate) may enter the waiting room;

e) Appropriate hand hygiene before entering the waiting room;

f) Temporal distancing of the tests, with lengthening of the schedule and remodelling of the appointments diary in accordance with the medical facility's specific procedures and according to the possibilities in the Department (waiting room, room, and personnel available for the examination).

g) The rooms where the lung function testing is carried out must be distinct from those used for the medical examination. It should be guaranteed that these rooms and the instrument kit used are sanitised according to enough of the European Centre for Disease Prevention and Control - ECDC sanitisation standards [16].

In the management of patients accepted for lung function testing, the patients are evaluated individually (one patient per dedicated room, easily sanitised), and:

a) patients are subjected to disinfection using hand gel

b) patients are instructed not to touch anything* unless specifically requested to do so

c) open the single use kit in the presence of the patient (antimicrobial filter**, connecting rubber mouthpiece, nose clips)

d) then explain the correct use

**here instrumentations with a support arm for the pneumotachograph or a flow meter are preferred*

***With specifications of great effectiveness (Nelson Test filtration >99%, proven effectiveness at high flow ≥600-700*

L/min, low resistance <1.5 cm$H_2O \cdot L^{-1} \cdot s$) whose application is further strengthened by using the "anatomical" rubber

mouthpiece connected to the filter in order to avoid disconnection during the manoeuvres and is a guarantee against

cross-contamination and emission of exhaled breath into the environment during the forced manoeuvres. In the case

of using disposable devices t, certainly preferable, it is also essential to remember that only interposing the abovementioned

antimicrobial filter safeguards the external environment and the health professionals during the spirometric
manoeuvres, above all if forced.
Whenever patients are self-sufficient and over 18 years of age, they are provided with surgical masks or masks certified as having the equivalent filtration and must enter the department without any companions. Should the patient needs a companion, this must limited to one individual companion per patient who has been subjected to pretriage
evaluation with their body temperature having been taken and an anamnesis in order to guarantee appropriate prevention of viral diffusion and prevent access to the department if the pre-triage evaluation suspects a virus. Particular and prudent attention should be paid to immunodepressed patients, transplanted subjects, and those with oncohaematological pathologies or fragile, and they should access the waiting room and medical facility by the dedicated entrance or more practically be examined at the start of the working session in order to avoid any possibility of contact with other users.

INDICATIONS FOR LUNG FUNCTION TESTING IN PHASE 2

a) Preoperative evaluation for thoracic and abdominal procedures
b) Pre-transplant evaluation
c) COPD (for the diagnosis)
d) Asthma (to evaluate presence of obstruction when clinically necessary)
e) Interstitial lung disease (ILD) in assessment (obligatory for the prescription of antifibrotic drugs and during follow up)
f) “Post COVID” evaluation of patients symptomatic for dyspnea (on exertion), or in health facility protocols, or observational examinations

For obvious reasons of a certain degree of containment of the request and safety and strengthening of the system in this phase, lung function testing must ideally be prescribed directly by the pulmonologist using a “level II appointments diary” (self-booking). This action means MMG is not possible nor may other specialists prescribe lung function testing. Therefore, it is suggested that this possibility is agreed with the institutions, at least temporarily, so that the indication is made correctly and both the longest time to carry it out and the waiting list are taken into consideration.

LUNG FUNCTION TESTING IN PHASE 2

Laboratory Personnel must be provided with PPE, that is, FFP2, fabric-non fabric smock, protective glasses, non-sterile gloves (for each patient).
The measurements that may be carried out according to the scientific societies ATS/ERS [7-8, 17-18] and the medical facility procedures in the pre-COVID-19 era are now listed:

-Slow Flow-Volume Manoeuvre
-Forced Flow-Volume Manoeuvre
-Measurement of the Functional Residual Capacity (FRC)* using N_2 washout technique
-Measurement of the CO diffusion capacity (DLco)
-Estimate of FRC from the Alveolar Volume with correction (19)
-Measurement of the Respiratory Resistance using oscillometry (Forced Oscillations, by Impulse) or by flow interruption [20] since periodic disinfection of the instrumentation can be carried out according to the manufacturer's instructions downstream from the antimicrobial air filter.
-Walking Test in ambient air (the patient wears the certified surgical mask and respects social distancing) in areas appropriately set up where other patients do not stay or on a rolling mat in a dedicated room.
-Arterial blood gas analysis (the patient wears the certified surgical mask)
**This leads to an increase in the times compared to the plethysmography technique, particularly in case of marked airway obstruction or in case of reversibility testing or when followed by DLco because of the inhalation of O_2*

In contrast, the following procedures require particular caution [2, 21-23]:

-Measurement of the Thoracic Gas Volume (TGV) using plethysmography technique because sanitisation of the box needs to be guaranteed. The measurement of the pulmonary volumes using this technique is considered to be the gold standard and is a significant saving of time [17]. The manufacturers suggest that the handle, seat, and all that is downstream of the antimicrobial air filter should be disinfected after each patient. All of this involves a significant expenditure of time between one examination and the next, and by personnel authorised to carry out the procedure.
-Bronchial challenge test using methacholine [24]. This results in evident environmental aerosolisation (multiple forced manoeuvres, increase in environmental volume during the methacholine aerosol) in addition to needing

appropriate procedures to disinfect the kit used for the nebulisation. Of all the above-mentioned examinations, this one certainly has the worst risk/benefit analyses, and it is not immediately necessary to set up a treatment. By evaluating instrumentation that facilitates the application of environmental filters for the challenge test, which is analogous to the above-mentioned antimicrobials as well as single-use disposable kit. The mannitol test (indirect bronchoprovocation test), not aerosol generating, should be evaluated for its applicability. As suggested in the ERS document [2], recourse to negative pressure chambers should also be evaluated. However, the compatibility of airflow caused by the negative pressure system using the stability of the spirometry sensor measurements needs to be verified. It has been demonstrated that 12 cycles of air an hour guarantee an exchange of 99% in 20-35 minutes [25], that is, an appropriate environmental sanitisation between the patients in the various sessions. Personnel in all cases should wear high quality PPE (FFP3, impermeable single-use aprons, eye protection, non-sterile gloves), that is, PPE prescribed for manoeuvres capable of generating aerosol.

-Cardiopulmonary exercise test (CPET). Although the measurement of VO_2 represents the gold standard [26] in preoperative examination of patients, according to Brunelli et al. [27] the possibility of substitution with the shuttle or stair-climbing tests should be evaluated for the same reasons as explained above. Although not indicated by the manufacturers, possibly adopting the above-mentioned antimicrobial air filters, which may however cause a change in the value measured, should be considered. Here too, laboratory personnel in all cases should wear high quality PPE, that is, PPE prescribed for manoeuvres capable of generating aerosol (FFP3, impermeable single-use aprons, visors, non-sterile gloves).

-Adaptation to CPAP/Bi-Level. This involves environmental aerosolisation. The problem is quite complex and specific, and requires dedicated documents.

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Other:

Measurement of exhaled nitric oxide (FE_{NO}) needs the interposing of a filter with the above-mentioned specifications. Bronchodilation test using pharmaceutical drugs. Bronchodilator medications can be inhaled using a distancing chamber equipped with a unidirectional valve and are single-use or disinfectable or use only plastic components (use and throw away) in the pressurised device.

Walking test and arterial blood gas analysis during O_2 administration. High level PPE is necessary just as for the other procedures capable of generating aerosol [21].

It is inadvisable to use sealed circuit systems for measurement of FRC by helium dilution technique since it is not easily accessible for periodic disinfection.

LUNG FUNCTION TESTING IN POST-COVID-19 PATIENT FOLLOW UP

At the time of writing there is only one article in the literature [28] that reports the results of a controlled randomised trial on the effects of respiratory rehabilitation on the respiratory function after 6 weeks. This study was carried out on elderly Chinese patients with established and confirmed diagnosis of COVID-19. FEV_1, FVC, FEV_1/FVC, DLCO, and 6-min walking test were used as Primary outcome measures. At the same time, the British Thoracic Society (BTS) guidance outlines recommend respiratory follow up of patients with a clinical-radiological diagnosis of COVID-19 pneumonia [29]. The same document emphasises the problem of long-term post-COVID-19 respiratory complications whose actual extent is unknown at the time of writing but on the basis of previous experience with survivors of the global SARS outbreak caused by SARS-CoV and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) will certainly be relevant. In fact, the literature from those years reports that, according to the various case histories, between 20% and 60% of survivors have shown persistent physiological impairment and abnormal radiology consistent with pulmonary fibrosis during follow up [30-32]. Starting from these experiences, in the current BTS document, inserting full lung function testing and the walking test with assessment of oxygen saturation in the follow up of post-COVID-19 patients is indicated. Not only pulmonary fibrosis but also pulmonary embolism and pulmonary hypertension are indicated as being worthy of consideration as sequelae.

LUNG FUNCTION TESTING IN COVID-19 CLINICAL TRIALS

Many clinical trials conducted on patients affected by respiratory diseases and those affected by systemic pathologies with pulmonary involvement provide for lung function testings for the selection of patients to be included in the trial or the evaluation of the effectiveness of drugs or treatment tested. Suspending the lung function testing planned in phase 2 is appropriate. To then complete the trials in progress or to assign new protocols, it is necessary to take into consideration the additional precautions to be taken for patient and operator safety, which are more cumbersome in COVID times and inevitably delaying work in pulmonary laboratories. It is therefore necessary to find a balance between the diagnostic workup priorities of the patients and those of scientific research. The lung function testing that are usually included in these trials are the Slow and Forced Flow-Volume manoeuvre and the DLco measurement

NOTES

Sanitisation of the pulmonary Laboratory. Activating action plans in the department to provide systematic and safe

sanitisation of an environment that, independently of COVID-19, has an intrinsic biological risk such as the application of UV lamps, use of hydrogen peroxide, ozone, or other forms of disinfection e.g. between morning and afternoon sessions and during the night. The ERS document advises against the use of anti-particulate filter systems which are

highly effective (HEPA) as they could become sources of viral colonisation [2]. It is also necessary for any administrative areas where computers dedicated to other procedures to be kept apart from the operational area where only the biomedical staff and the computers dedicated to them should be present.

Research and development. This document aims to draw attention to the need for researchers and manufacturing companies to find solutions for: a) rapid, efficient, automated sanitisation of the plethysmography box among patients; b) validation of the use of antimicrobial filters during the cardiopulmonary exercise test (CPET); c) use of the forced oscillation technique in the bronchoconstriction test; d) validation of the above-mentioned antimicrobial filters by measuring the nitric oxide in the exhaled breath (FE_{NO}); e) development plans for providing Territorial Simple Spirometry ensuring the implementation of the safety measures described and constant specialist quality control.

CONCLUSION

Maximum safety of pulmonary laboratories is required in the COVID-19 era and for future reference, dedicating personnel ad hoc, and empowering dedicated full-time medical directors and managers.

AUTHOR CONTRIBUTIONS

All the authors wrote and edited the manuscript.

DECLARATION OF COMPETING INTEREST STATEMENT

The authors declare no conflict of interest.

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