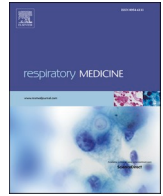




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Review article



Suggestions for lung function testing in the context of COVID-19

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ABSTRACT

The 2019 coronavirus disease (COVID-19) pandemic is currently a challenge worldwide. Due to the characteristics of lung function tests, the risk of cross infection may be high between health care workers and patients. The role of lung function testing is well defined for the diagnosis of various diseases and conditions. Lung function tests are also indispensable in evaluating the response to medical treatment, in monitoring patient respiratory and systemic pathologies, and in evaluating preoperative risk in cardiothoracic and major abdominal surgeries. However, lung function testing represents a potential route for COVID-19 transmission, due to the aerosol generated during the procedures and the concentration of patients with pulmonary diseases in lung function laboratories. Currently, the opportunities for COVID-19 transmission remain partially unknown, and data are continuously evolving. This review provides useful information on the risks and recommendations for lung function testing, which have varied according to the phase of the pandemic. This information may support national and regional boards and the health authorities to which they belong. There is a need for rapid re-opening of lung function laboratories, but maximum safety is required in the COVID-19 era.

1. 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 represents a potential means of COVID-19 transmission, due to the concentration of patients with pulmonary diseases in lung function laboratories and due to the potential

generation of aerosols during the procedures. Moreover, for the patients it is not possible to wear surgical masks during spirometry operating procedures, and the duration of patient contact with the operator is > 15 min. This is a common problem for otolaryngologists, specialists, and dentists, who experience similar types of exposure [3]. Although most patients are screened for COVID-19 symptoms prior to admission to health care units, patients with respiratory diseases may exhibit symptoms comparable to those associated with a COVID-19 infection.

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Nomenclature

SSD	Struttura Semplice Dipartimentale
ASL(Azienda Sanitaria Locale-Ospedale/unità operativa igiene e sanità pubblica)	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
UOC (Unità Operativa Complessa)	Multispecialty Department
IRCCS (Istituto di Ricovero e Cura a carattere scientifico)	Hospital for excellence in clinical research and provision of health services. Both public and private
AOU (Azienda Ospedaliera Universitaria)	University Hospital Trust
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
Fondazione IRCCS (Istituti di Ricovero e Cura a Carattere Scientifico)	Scientific Institute for Research, Hospitalization and Health Care
AUSL(Azienda Unità Sanitaria Locale)	Local Area Health Authority Unit
SOS (struttura operative semplice)	Department, Division, or Unit in a hospital
ASP (Azienda di Sanità Pubblica)	Local/Provincial Public Health Care Authority

Opportunities for COVID-19 transmission remain unknown, and the data are continuously evolving. The risk of transmission varies with the prevalence of the virus in the community, the subject's age, the seriousness of the pulmonary disease, and the presence/absence of immunosuppression. Consequently, the recommendations made by the ERS [2] are useful. They have varied according to the phase of the pandemic. In phase 1 of the pandemic, they recommended a total suspension of lung function testing, and tests were limited to preoperative evaluations only. In the "post-peak" phase of the pandemic, those services were allowed to restart, with maximum safety constantly in mind. Lung function testing can only proceed according to "standard" precautions, when the viral presence is low, and when rapid, reliable methods are available to evaluate contagiousness, based on a combination of symptom 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, and sleep-related breathing disorders. For some diseases, like interstitial lung disease (ILD), it is better to evaluate the clinical picture. Lung function testing is also indispensable in evaluating the response to medical treatment, in following patients with pulmonary or systemic pathologies that feature pulmonary involvement, and in evaluating preoperative risk in thoracic and abdominal surgeries, with a view towards adding the patient to the transplant list. In particular, functional evaluations of COPD are desirable, because the late diagnosis of this disease incurs high socio-health-related costs.

For some time, it has been noted that, in lung function laboratories, there are several more or less high-risk sources of cross-infection between patients and operators. Numerous studies and ERS/ATS workshop reports have been published since the 1990s that provided accurate information about the prevention and control of viral/bacterial

infections [4–6]. Then, in 2005, the official ATS/ERS document on the standardisation of respiratory functionality examinations was published. The chapter entitled "Hygiene and infection control" [7], which was updated in 2019 [8], represents the current official guideline. Since then, it has been imperative for all laboratories to have a policy that includes all aspects of infection control, including methods for washing, sterilising, and using protective equipment and the implementation of specific personnel training. Moreover, other in-depth research studies and updates have been published in recent years to emphasise the need for constant control of infection [9,10]. The current COVID-19 epidemic and the need to re-open lung function laboratories have led to the need for a dramatic revision, particularly of documents currently available. Moreover, we must rethink many 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, even though, currently, the virus characteristics are not fully understood [11,12].

A recent ATS document [1] has emphasised the intrinsic risk of spirometric manoeuvres that are capable of generating aerosol. At the time of writing this review, only one international study has confirmed the risk involved in spirometric manoeuvres when managing patients with allergy and immunological diseases [13]. The risk from spirometric manoeuvres was also underlined in a Global Initiative on Asthma [14], which suggested ways of limiting the diffusion of the virus in ambulatory environments; those suggestions were useful for the purposes of this review.

Another theme we will cover is the sanitisation of instrumentation required for nocturnal cardiorespiratory monitoring, in light of the COVID-19 pandemic. The complex problems of management of patients with Obstructive Sleep Apnoea Syndrome require respiratory support [15], need further specific and in-depth study.

This review aimed to provide several specific recommendations on the control of infections when conducting lung function testing, in the new context caused by COVID-19. These recommendations should be considered an extension to the recommendations for all infections previously codified in the 2005 official document [7], which was updated in 2019 [8]. These recommendations have become indispensable for patients with appropriate indications, in view of the re-opening of lung function laboratories, in the so-called COVID-19 phase 2 (post-peak) era. It is also extremely important that these recommendations are considered in view of the new follow up studies planned for patients in "post-COVID" status, where lung function tests are necessary to evaluate residual functional damage.

This review focused on the need to identify patients with indications for spirometry in COVID-19 phase 2. We also focused on the need to take all possible reasonable actions to exclude an active infection before patients enter the laboratory, according to protocols determined by individual medical facilities and departments (e.g., making telephone contact 24–48 h before the appointment and performing triage immediately before entering the medical facility).

2. General warnings

Medical practices must be accessed through well-defined entrances that can be reached easily (also sign-posted). This protocol will guarantee controlled flows and reduce the time that patients spend inside the facility to a minimum. In addition to the time required to carry out lung function testing, it is necessary to calculate air exchange and air replacement with fresh air for approximately 15 min, in accordance with ERS guidelines.

3. Specific warnings

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

- A pre-triage telephone call should be made to avoid allowing patients with suspicious symptoms access to the waiting room; the call should be made as close as possible to the date of service (i.e., 24–48 h prior to the appointment) [see appendix].
- Nasopharyngeal swab samples should be collected from patients with suspected COVID-19, 48–72 h before the respiratory functional exam.
- The patient should be received with attention to social distancing (legal regulations); body temperature should be measured; and a targeted anamnesis should be recorded.
- Only patients (and any companions) with a surgical mask (or equivalent mask with filtration certificate) may enter the waiting room.
- Appropriate hand hygiene should be performed before entering the waiting room.
- Tests should be distanced temporally, by extending the appointment time and revising the appointment diary to conform to the medical facility's specific procedures and the capacity of the Department (i.e., waiting room, examination rooms, and personnel available for the examination).
- The rooms for conducting the lung function tests must be distinct from the rooms for medical examinations. These rooms and the instrument kit used should be sanitised according to the sanitisation standards established by the European Centre for Disease Prevention and Control [16].

When managing patients accepted for lung function testing, each patient should be evaluated individually (one patient per dedicated room, which can be easily sanitised), and:

- patients should be subjected to disinfection with hand sanitising gel;
- patients should be instructed not to touch anything*, unless specifically requested to do so;
- the single-use kit should be opened in the presence of the patient (the kit should contain an antimicrobial filter**, a connecting rubber mouthpiece, and nose clips);
- the clinician should clearly explain the correct use of the kit.

*here, instruments with a support arm for the pneumotachograph or a flow meter are preferred.

**Filters with specifications of high effectiveness (Nelson Test filtration >99%, with proven effectiveness at high flow of ≥ 600 – 700 L/min, low resistance of < 1.5 cmH₂O·L⁻¹·s); the filter is further strengthened by using the “anatomical” rubber mouthpiece connected to the filter, which prevents disconnections during the manoeuvres. The filter and mouthpiece prevent cross-contamination and environmental contamination due to exhaled emissions during the forced manoeuvres. When using disposable devices, which are certainly preferable, it is essential to remember that the external environment and the health professionals can only be safeguarded by interposing the antimicrobial filter during the spirometric manoeuvres, particularly when manoeuvres are forced.

All patients that are self-sufficient and over 18 years of age are provided with surgical masks, or masks certified to provide equivalent filtration, and they must enter the department without any companions. If the patient needs a companion, they are limited to one individual companion per patient, and the companion must be subjected to the pre-triage evaluation with a body temperature measurement and an anamnesis recorded. This procedure is necessary to guarantee appropriate prevention of viral diffusion. When the pre-triage evaluation indicates a suspected viral infection, the infected individual must be denied access to the department.

Particular and prudent attention should be paid to patients that have received immunosuppressants, a transplantation, a diagnosis of an oncohaematological pathology, or a fragile status assessment. These patients should access the waiting room and medical facility through a

dedicated entrance, or more practically, they should be examined at the start of the working session to avoid any possibility of contact with other patients.

4. Practical recommendations for the protection of healthcare workers during lung function testing

Healthcare workers that assist or guide the patient during the functional examination are at high risk of contracting an infection. The goal of infection control is to prevent both patients and staff from becoming infected during lung function testing. Before the COVID-19 pandemic, only a very small number of infection transmission cases were documented, but the potential has been considered real in specific official documents. They have always emphasised the need for operators to observe safety precautions (7-8). The rapid spread of COVID-19 and the global threat that has pushed health care capacities to their limits have demanded more intense surveillance.

First, technicians need to be familiar with the theory and practical aspects of disease and infection control measures. Infection can be transmitted by direct contact with surfaces, such as mouthpieces, nose clips, handheld spirometers, chair arms, and valves or tubing. Indirect transmission occurs by deposits of the aerosol generated when a patient blows into the equipment; additionally, between manoeuvres, breathing can expel aerosols into the air of the testing room. Laboratory personnel must use personal protective equipment, such as filtering facepiece class 2 (FFP2) or FFP3 masks (when performing aerosol-generating procedures), a fabric or non-fabric smock, protective glasses, and non-sterile gloves.

5. Indications for lung function TESTING in phase 2

In phase 2 of the pandemic, patients should only be tested for lung function under the following conditions:

- Preoperative evaluations for thoracic and abdominal procedures
- Pre-transplant evaluations
- COPD diagnoses
- To evaluate the presence of obstruction in patients with asthma (when clinically necessary)
- To assess ILD (obligatory for prescriptions of antifibrotic drugs and during follow up)
- A “post COVID” evaluation for patients with symptoms of dyspnoea (on exertion), or when required in health facility protocols, or for observational examinations

For obvious reasons, a certain degree of containment is required to ensure personal safety and to strengthen the system in phase 2 of the COVID-19 pandemic. Ideally, lung function testing must be prescribed directly by the pulmonologist, with a “level II appointments diary” This action rules out the possibility of general practitioners, and prevents other specialists from prescribing lung function testing. Therefore, it is suggested that this action should be agreed upon between institutions, at least temporarily. This action would assure that the indication is made correctly, that the longest possible delay is considered, and that the waiting list is taken into consideration.

6. Lung function testing in phase 2

The ATS/ERS scientific societies [7,8,17,18] and medical facility procedures have established that the following measurements can be carried out in the pre-COVID-19 era:

- Slow Flow-Volume Manoeuvre
- Forced Flow-Volume Manoeuvre
- Measurement of the Functional Residual Capacity (FRC)* with the N₂ washout technique

- Measurement of the CO diffusion capacity (DLco)
- Estimation of the FRC from the Alveolar Volume, with correction [19]
- Measurement of the Respiratory Resistance with oscillometry (Forced Oscillations, by Impulse) or with flow interruption [20], because the instrumentation can be periodically disinfected, according to the manufacturer's instructions, downstream of the antimicrobial air filter.
- Walking Test in ambient air (the patient wears the certified surgical mask and respects social distancing) in areas set up appropriately, where other patients are not allowed to linger, or on a rolling mat in a dedicated room.
- Arterial blood gas analysis (the patient wears a certified surgical mask)

*This procedure leads to an increase in the examination time, compared to the plethysmography technique, particularly in patients with marked airway obstruction, in cases of reversibility testing, and when followed by DLco, due to the inhalation of O₂

The following procedures require particular caution [2,21–23]:

- **Thoracic Gas Volume (TGV) measurement.** TGV when measured with the plethysmography technique, requires sanitisation of the box after each patient. Measuring pulmonary volumes with this technique is considered to be the gold standard, and it saves a significant amount of time [17]. The manufacturers recommend disinfecting the handle, seat, and all the parts downstream of the antimicrobial air filter after each patient is measured. This disinfection procedure requires a significant time expenditure between examinations, and it requires personnel authorised to carry out the procedure.
- **Bronchial challenge test with methacholine [24].** This test results in evident aerosolisation into the environment, due to the multiple forced manoeuvres required and exhalation of the current volume during methacholine aerosol. In addition, appropriate procedures are needed to disinfect the kit used for the nebulisation. Among all the examinations mentioned above, this test certainly has the worst risk/benefit ratio. Alternatively, the mannitol test (indirect bronchoprovocation test), which does not generate aerosol, should be evaluated for its applicability. The ERS document [2] suggests that negative pressure chambers should also be evaluated. However, the compatibility of airflow caused by the negative pressure system with the stability of the spirometry sensor measurements needs to be verified. It has been demonstrated that 12 cycles of air per hour guarantee the exchange of 99% of the room air in 20–35 min [25]. That is, for appropriate environmental sanitisation, a 20–35 min waiting interval should be imposed between patient sessions. In all cases, all personnel should wear high quality personal protective equipment (PPE), including a FFP3 mask, an impermeable single-use apron, eye protection, and non-sterile gloves. This PPE is prescribed for manoeuvres capable of generating aerosols.
- **Cardiopulmonary exercise test.** The measurement of VO₂ represents the gold standard [26] for measuring cardiopulmonary performance in preoperative examinations, according to Brunelli et al. [27]. However, the possibility of substituting this test with either the shuttle or stair-climbing test should be evaluated, for the reasons explained above. Although not recommended by the manufacturers, clinicians should consider the possibility of adopting antimicrobial air filters (see **note in SPECIFIC WARNINGS); however, using a filter might cause changes in the values measured. Here too, in all cases, laboratory personnel should wear high quality PPE, which is prescribed for manoeuvres capable of generating aerosol (i.e., FFP3, impermeable single-use aprons, visors, and non-sterile gloves).
- **Adaptation to continuous positive airway pressure (CPAP) or Bi-Level PAP.** This procedure generates aerosols that are released into the environment. The problem is quite complex and specific; thus, it requires dedicated documents.

Other:

- **Exhaled nitric oxide (FENO) measurement.** This procedure requires the interposition of a filter with the above-mentioned specifications (see **note in SPECIFIC WARNINGS).
- **Bronchodilation test with pharmaceutical drugs.** Bronchodilator medications can be delivered by inhalation from a pressurised, metered-dose inhaler, equipped with a distancing chamber and a unidirectional valve. These inhalers are either single-use (disposable) or they can be disinfected.
- **Walking test and arterial blood gas analysis during O₂ administration.** High-level PPE is necessary when performing this procedure, as described above for other procedures that generate aerosol [21].
- **FRC measurement with the helium dilution technique.** It is inadvisable to use sealed circuit systems for this procedure, because they are not easily accessible for performing periodic disinfections.

7. Lung function testing in post-covid-19 patient follow UP

At the time of writing this review, only one previous study [28] reported the results of a controlled randomised trial that tested the effects of respiratory rehabilitation on respiratory function after 6 weeks. That study was carried out on older Chinese patients with established and confirmed COVID-19 diagnoses. The primary outcome measures were the forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), FEV₁/FVC, DLco, and the 6-min walking test. At that time, the British Thoracic Society (BTS) guidelines recommended a respiratory follow up for patients with a clinical-radiological diagnosis of COVID-19-related pneumonia [29]. That recommendation emphasised the problem of long-term post-COVID-19 respiratory complications. Although the actual extent of complications was unknown at that time, they were considered relevant, based on experiences with survivors of previous global outbreaks of Severe Acute Respiratory Syndrome and the Middle East Respiratory Syndrome, which were both caused by a coronavirus. In fact, the literature from those years reported that, according to various case histories, between 20% and 60% of survivors showed persistent physiological impairments and abnormal radiology, consistent with pulmonary fibrosis, during follow up [30–32]. Starting with those experiences, the current BTS recommendations included full lung function testing and the walking test with an assessment of oxygen saturation when patients were followed up after a COVID-19 infection. In addition to pulmonary fibrosis, pulmonary embolism and pulmonary hypertension are considered potential sequelae.

8. Lung function testing in COVID-19 clinical trials

Lung function tests are performed in many clinical trials that evaluate drug or treatment effectiveness in patients affected by respiratory diseases or systemic pathologies with pulmonary involvement. Lung function testing is performed to select patients for trial inclusion. Currently, it has been deemed appropriate to suspend lung function testing in trials planned to commence in phase 2 of the COVID-19 pandemic. However, to complete the trials in progress or to assign new protocols, it is necessary to take into consideration additional precautions to maximise patient and operator safety. These precautions are more cumbersome in the COVID era than in previous eras, and inevitably, they cause work delays in pulmonary laboratories. Therefore, it is necessary to find a balance between the priorities of a diagnostic workup and the priorities of scientific research. The lung function tests typically included in these trials are the Slow and Forced Flow-Volume manoeuvre and the DLco measurement.

9. Notes

Sanitisation of the pulmonary Laboratory. Action plans in the

department should provide systematic, safe sanitisation between morning and afternoon sessions and during the night. This is complicated in an environment that, independent of COVID-19, presents intrinsic biological risks, such as UV lamp applications and the use of hydrogen peroxide, ozone, or other forms of disinfection. The ERS advises against the use of anti-particulate filter systems, like high-efficiency particulate air filters, because they might become sources of viral colonisation [2]. It is also necessary to separate all administrative areas, where computers dedicated to other procedures are located, from the operational area, where only the biomedical staff and the computers dedicated to them should be present.

Research and development. This document aimed to draw attention to the need for researchers and manufacturing companies to find solutions for: a) rapid, efficient, automated sanitisation of the plethysmography box between patients; b) validating the use of antimicrobial filters during the cardiopulmonary exercise test; c) applying the forced oscillation technique in the bronchoconstriction test; d) validating antimicrobial filters (see **note in SPECIFIC WARNINGS) by measuring the FE_{NO}; e) developing plans for providing Territorial Simple Spirometry that ensures the implementation of the safety measures described and constant specialist quality control.

10. Conclusion

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

Author contributions

All authors contributed to writing and editing the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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