Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

COVID-19 and respiratory support devices

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Educational aims

The reader will be better able to understand that:

- Reallocation of resources is needed to supply essential medical equipment during an epidemic outbreak.
- The development and use of emergency devices for respiratory support is a complex interaction between healthcare providers, patients, and the respiratory support devices.
- It is essential to implement appropriate procedures to rapidly evaluate new medical devices; including the testing and training using animal models that replicate human disease.

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ABSTRACT

There are significant logistical challenges to providing respiratory support devices, beyond simple oxygen flow, when centres run out of supplies or do not have these devices at all, such as in low resource settings. At the peak of the COVID-19 crisis, it was extremely difficult to import medical equipment and supplies, because most countries prohibited the medical industry from selling outside of their own countries. As a consequence, engineering teams worldwide volunteered to develop emergency devices, and medical experts in mechanical ventilation helped to guide the design and evaluation of prototypes. Although regulations vary among countries, given the emergency situation, some Regulatory Agencies facilitated expedited procedures. However, laboratory and animal model testing are crucial to minimize the potential risk for patients when treated with a device that may worsen clinical outcome if poorly designed or misused.

The experience in caring for hospitalized children with COVID-19 in Barcelona, like in many other places, has fortunately been very limited. This allowed us to support and initiate projects developing respiratory support devices in our region. At the beginning of the outbreak, there was an alarming message regarding the potential need for thousands of ventilators. In areas with the highest impact of the outbreak, the number of intensive care unit [ICU] beds multiplied threefold. This article shares strategies implemented in Catalonia, Spain, to provide respiratory support to the vast number of adult patients admitted to our hospitals with respiratory failure.

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VENTILATOR RESOURCE USE

Initially, many hospitals were able to convert operating rooms and general wards into ICUs using anaesthetic ventilators, transport ventilators, and older ventilators coming from laboratories or teaching simulation areas. Non-invasive ventilators have also been used transiently as invasive ventilators in pressure-controlled modes. However in some hospitals, these resources were rapidly exhausted.

In Spain, the National government provides most of the healthcare resources and the regional authorities regulate their use. Catalonia is situated in the North East corner of the country, with Barcelona as its capital. The local government undertook several key initiatives as listed in Tables 1 and 2.

REDEPLOYMENT AND RETRAINING OF STAFF

In Spain, as in other countries, most General Hospitals redeployed clinicians, including paediatricians, trainees, and nurses to care for adults with respiratory failure due to COVID-19. Each of these healthcare professionals was incorporated into an adult care team to work under an adult intensivist's supervision. As a Children's Hospital, Hospital Sant Joan de Déu received paediatric patients from General Hospitals, which transformed all their paediatric wards, including PICUs, to treat adult COVID patients. During the worst period of the outbreak in Barcelona, our PICU adapted one room ten-bed PICU area for several weeks. At the epidemic peak, 16 adult COVID-19 patients were admitted. Although some patients were transferred from the Emergency Department of a General Hospital, most were transferred from adult ICUs when beds were needed for new urgent admissions. It was challenging for the team to continuously update protocols of care to manage adults with underlying chronic disorders rarely seen in paediatrics such as essential hypertension, COPD and morbid obesity.

DEVELOPMENT OF IMPROVISED AND INNOVATIVE TECHNOLOGIES

There are significant logistical challenges to providing respiratory support devices, beyond simple oxygen flow, when centres run out of supplies or do not have these devices at all, such as in low resource settings. At the peak of the COVID-19 crisis, it was difficult to import medical equipment and supplies because most countries prohibited their medical industry from selling outside their own countries. Even helmet interfaces, the safest option according to experts [1], could not be imported because of government restrictions.

The authors were involved in supporting the Hospital's Innovation Department engineers in developing a CPAP device with a PEEP valve and a Venturi connector fitted to a facial snorkel interface, as previously used by Italian doctors [2]. This device, called ECPAP, was recently approved by the Government agency that certifies medical products, Agencia Española del Medicamento y Productos Sanitarios (AEMPS), to conduct clinical safety studies. The initial purpose in developing this system was to offer an alternative interface to adult full-face or oro-nasal masks if these were not available. Face masks can reduce droplet dispersion and consequently decrease the risk of infection to healthcare workers [1].

Recently, a team from our University developed a low-cost bilevel turbine-based ventilator for non-invasive ventilation (NIV) support, which was published as an open access article to allow all interested to see the technical description [3]. This ventilator compared favourably against a commercial device in a pilot study of healthy subjects instrumented to mimic respiratory diseases. Remarkably, it has been shown that CPAP and NIV allowed many patients to avoid intubation by using the algorithm developed in Italy, which included a short trial on CPAP [4].

In the most severe cases requiring invasive ventilation, the simplest way to proceed could be the use of a bag resuscitator. However, the use of bag resuscitators for hand ventilation showed significant variability in the tidal volume provided [5]. A randomized controlled trial comparing transport ventilators to hand bag ventilation showed that transport ventilators were significantly better in achieving the volume target [6]. Thus, hand bag ventilation should not be used except for short periods of ventilation. Accordingly, enthusiastic teams of engineers worldwide responded to the challenge to build devices that could provide respiratory support to COVID-19 patients. A variety of automated bag devices, called by FDA emergency use resuscitator systems (EURS), were developed as a result. In Spain, AEMPS facilitated a procedure to permit the use of alternatives devices without the Conformity European [CE] mark for compassionate clinical studies in COVID-19 patients. The authors had the chance to evaluate the performance of several emergency ventilators and a split device using an acute respiratory distress syndrome (ARDS) animal model. The split ventilation prototype, although capable to regulate and monitor the tidal volumes of the two different animals, could not proportionate different levels of PEEP and maintain both animals' stability when changing one of the animal's compliance.

Even though some of these devices may become available, there is no guarantee that they will provide optimal ventilation. Especially for invasive ventilation, the need for an appropriate environment with a trained staff is crucial to good outcomes. Indeed, clinical experience in Bangladesh, having an 80% mortality in pneumonia patients mechanically ventilated in the PICU, prompted a RCT [7] which showed superior results using the simplicity and safety of bubble CPAP, a device that can be built locally at low cost [8].

GOVERNMENT REGULATIONS

Most teams of engineers, who did not have biomedical backgrounds, concentrated on developing simple respiratory devices based on resuscitation bags requiring positive end-expiratory pressure (PEEP) valves. Companies with medical device experience, or academic centres, developed respiratory devices fulfilling most requirements for the device to be properly called a ventilator. Mechanical Ventilator Milano (MVM) is an example of the value of international collaboration between University centres and companies from Italy, Canada and the USA [9].

It is important to stress that new devices should initially be evaluated in a physiology laboratory using a lung simulator. In our case, most were evaluated at the School of Medicine of the University of Barcelona where the bi-level device previously men-

Table 1
Catalan Government initiatives.

- Companies were asked to urgently develop new devices to provide respiratory support.
- Home ventilation providers assembled home ventilators from their available supplies for hospital use. Patients not using their home CPAP devices had their devices redeployed to the hospitals for acute care.
- Companies were asked to provide oxygen to hotels that had been temporarily converted into convalescence hospitals and care units for mild patients.
- Veterinarians were asked to lend their ventilators, commonly old-fashioned, for human use, to be used for acutely ill patients.

Table 2
Catalan Government key respiratory support devices initiatives.

Project Name	Device	Type	Medical device class	Promoter
OxyGEN	EURS	Pressure	IIb	Protofy.xyz
Leitat 1–2	EURS	Pressure	IIb	Consorci de la Zona Franca (CZF), Leitat
RESPIRA	EURS	Pressure	IIb	GPA Innova
RESPIREM	EURS	Pressure	IIb	SECARTYS
Q-Vent	EURS	Pressure	IIb	H. Sant Pau
DAR		Volumetric	IIb	GASN2
Olot		Volumetric	IIb	Noel Alimentació
ECPAP	CPAP	Facial Mask	IIa	HSJD

tioned was developed. With minimal monitoring available in most of the EURS, it is important to ensure that the delivered tidal volume is accurate for diverse clinical conditions. According to the Spanish regulatory body (AEMPS), ventilator prototypes must then be tested in a porcine model, ideally suffering from ARDS. In collaboration with the Comparative Medicine and Bioimage Centre of Catalonia (CMCIB), belonging to the Research Institute Germans Trias i Pujol (IGTP), a COVID-19 ARDS scenario was developed in a pig model to test different devices. Animal numbers and procedures were approved by the Institutional Animal Care and Use Committee of the institution and the competent authorities (Protocol # 10945). An ARDS model was [10] with bronchoalveolar lavage and high tidal volume ventilation (10) until a PaO_2/FiO_2 ratio between 150 and 250 was achieved. With obesity being a common comorbidity in severe cases of COVID-19, we further tested the ventilator by adding a 10 kg weight on the abdomen of the supine animal to simulate the mechanical effects of obesity.

Advanced simulation with an animal model permits identification of possible pitfalls not apparent in the physiology laboratory. For example, evaluating an EURS with an external PEEP valve, we found that condensed humidity induced by respiration affected the behaviour of the PEEP valve, a phenomenon that could compromise patient oxygenation. Moreover, inappropriate settings can generate rebreathing or auto PEEP, which is a problem that can be missed in the laboratory but is easily identified by blood gas measurements in the animal during the *in vivo* testing procedure.

Importantly, each new emergency device will also require its own troubleshooting checklist which are likely different from those used for conventional ventilators available in hospitals. Therefore, it is crucial to have a clinician's guidance based on the problems observed in the laboratory and in the simulation with animals. No matter how acute the anxiety generated by the lack of ventilators is, connecting a patient to an insufficiently tested device may lead to morbidity which could be worse than not using the device at all. Additionally, a certification laboratory should assess safety issues and electromagnetic compatibility, similar to those required to get the CE label. Fortunately, even at the peak of the epidemic, the newly developed ventilators were not required for clinical use. Hence, checking their clinical performance in Spain was not possible as there was no ethical reason to justify this.

THE FUTURE: LOW-MIDDLE INCOME COUNTRIES MOVING BEYOND OXYGEN

We do have a unique opportunity to learn whether some of these relatively inexpensive and simpler COVID-19 inspired devices could play a role in low-middle income countries where mechanical ventilators are in short supply or simply unavailable. As mentioned before, ventilator support is not only a matter of having devices available. In Formula-1 racing it is possible to finish a race with only one car and driver. Nevertheless, to compete for the world championship requires having a seasoned driver, replacement car(s), and a support team trained with engineers, mechanics for maintenance, and the availability of spare parts for repairs. Providing effective mechanical ventilation therapy also requires a multi-disciplinary, well-trained team including health care staff and technical support people able to service the equipment.

It is time to offer more than oxygen from the concentrator, or low-cost devices to improve the outcome of respiratory failure in developing countries. Open source technology publication [11], co-creation design approaches involving local partners [8] and training modules for on-site healthcare workers, technicians, and engineers are needed to make a difference, which with sufficient commitment globally could finally bring about long-term improvements.

FUTURE DIRECTIONS FOR RESEARCH

- In low-middle income countries, due to the scarcity of CPAP devices or ventilators, conducting clinical studies with novel COVID-19 emergency devices could contribute to saving lives.
- To reassess the management of respiratory failure with affordable and straightforward devices to provide both non-invasive and invasive support.
- To evaluate the most effective and efficient ways to train healthcare providers from diverse settings to understand and correctly use novel devices.

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