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Global Impact of Mechanical Ventilators on COVID-19 Patients with Associated Comorbidities: A Review

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ABSTRACT

The genesis of coronavirus disease has led to 545481 confirmed deaths globally as recorded on July 10, 2020. It is quickly unfolding and evolving. Critically ill COVID-19 patients with or without other ailments are observed for intensive care. Immediate ventilation/oxygen supply is targeted on severe COVID-19 pediatric and adult cases with ARDS and related insufficiencies. Approximately 3.2% chronic cases required intubation and invasive mechanical ventilation while selected one are noninvasively ventilated. Variable advanced approaches employed during ventilation depending upon the complexity and need of carrier. Moreover, precautionary guidelines for the use of ventilators and self-protection should be strictly followed to prevent risks. This review will summarize the current literature and future aspects of worldwide clinical emergent applications of ventilators in COVID-19 pandemic. It is aimed to develop strategies with a hope to control the infection in upcoming future.

INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) Director-General announced Novel Coronavirus Disease, COVID-2019, a “global pandemic” [1]. World got into a panic emergency situation due to alarming levels of spread and severity. Coronavirus is an enveloped positive sense single stranded RNA virus (ranging from 60 nm to 140 nm in diameter). Spike like projections giving a crown like appearance on its surface, when observed under the electron microscope, justify the name coronavirus. It belongs to the Coronavirinae subfamily, part of the Coronaviridae family [2, 47]. On February 11, 2020, the carrier of disease was named as “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”. It is genetically related to the coronavirus responsible for the SARS outbreak of 2003 [40, 63]. It is assumed to be originated from bats but other reservoir intermediate hosts are unidentified. It is transmitted among individuals through coughing, sneezing and respiratory fomites when an adequate precaution of close contact from infected person is not considered [2, 43-45, 63].

First case was recognized on December 2019 in Wuhan, China. Patients were observed with respiratory tract infection caused by a newly emergent SARS-CoV-2 and Middle East respiratory syndrome coronavirus (MERS-CoV). Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus [20, 46]. The disease is transmitted by inhalation or contact with infected droplets and incubation period ranges from 2 to 14 days. Clinically features of COVID-19 are observed variable including symptomatic to asymptomatic conditions. Fever (uncommon), cough, sore throat, breathlessness, headache, fatigue, myalgia and malaise are mild in many patients, while in some patient common and severe complications of pneumonia, dyspnea, acute respiratory distress syndrome (ARDS), sepsis, septic shocks, and multi organ dysfunction or failure may occur [2, 3, 21, 32]. Hypertension, diabetes, cardiovascular disease, chronic lung disease, cancer, worse respiratory failure, higher d-dimer and C-reactive protein concentrations, lower lymphocyte counts, and secondary infections are major comorbidities among the infected older patients, increasing the risks of death [4-6, 22]. Critical illness and ultimately death may occur, if not treated carefully [2, 3, 22, 32]. At present, 11.9 million total confirmed positive COVID-19 cases are there with 216 affected countries [52]. In accordance with a protocol, it is reported that monitoring the patients utilizing mechanical ventilator positively affects clinical outcomes in severe patients [36].

MECHANICAL VENTILATORS:

A mechanical ventilator is an automatic machine used for the first time in 1929. It assists by improving and managing air or gas movement into the lungs, i.e., breathing. The device pushes airflow through a hollow tube (artificial airway) that goes into the patient's mouth and down into their main airway or lungs to help them breathe [8, 65].

Mechanical ventilation (MV) is the process by which gas moves in and out of the lungs. Although not accurately but, ventilation is often used interchangeably with respiration, which is refers to as the process of cells exchanging materials for homeostasis (it is a condition when oxygen and carbon dioxide are exchanged in the lung's alveolar capillary beds) [27].

CLASSIFICATION OF VENTILATION:

On the basis of frequency of breathing, ventilators may be conventional (produce low breathing rates) or high frequency ventilators (generate maximum breathing rates). Broadly, MV is of two types [27, 35, 23, 65]:

1. **Positive-pressure ventilation (PPV):** It is the most common form of MV used in hospitals. It delivers adequate oxygen with carbon dioxide expulsion. It pushes the air into the lungs using flexible tubes. Depending upon the tubes orientation (as shown in Fig 1), they are as follows:

a) **Invasive mechanical ventilation (IMV):** In this tracheostomy or endotracheal tube connected to the ventilator extends to the patient's throat (airway). They are widely recommended and available in three categories, viz., manual, portable and intensive care ventilators.

b) **Noninvasive ventilation (NIV):** It consists of mask which either cover the nose and mouth or only nose. It is recommended in unconscious patients.

2. **Negative-pressure ventilation (NPV):** In this ventilation either patient is placed entirely or partially inside a chamber for oxygenation. It works by sucking the air into the lungs by making the chest expand and contract.

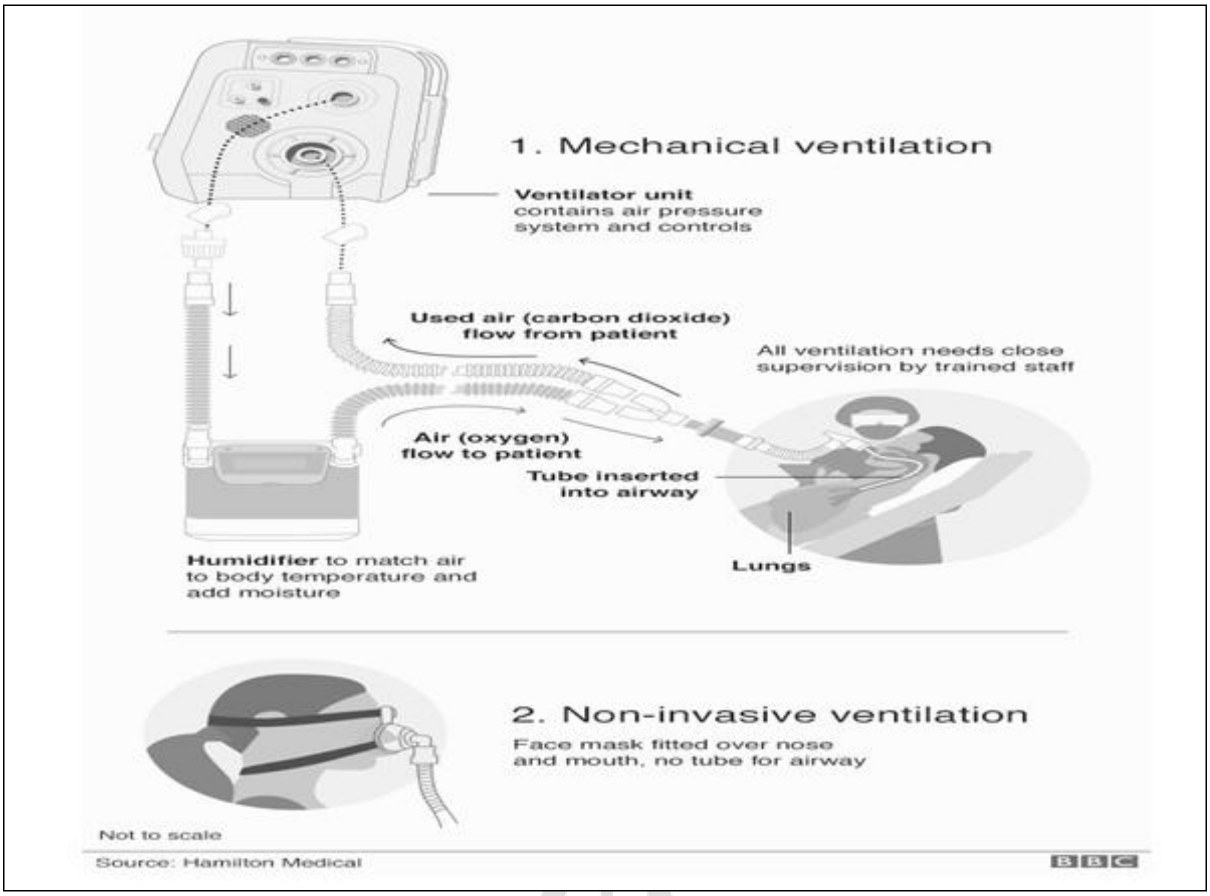

Figure No. 1: Illustration of types of MV according to connectivity of tubes [23]

GENERAL USES:

Nearly every other patient in various emergency situations is undergoing MV. These critical patients have a variety of disorders that may require intubation and IMV. Most of them are respiratory emergencies related with ARDS, pneumonia, asthma, chronic obstructive pulmonary disease. The current evidence supports the use of NIV for these patients (especially in COPD), but IMV also is required frequently in patients who have more severe disease like cardiogenic pulmonary edema, congestive heart failure, spinal cord injury, stroke, trauma, severe sepsis, shock, myasthenia gravis including cases from intoxication, drug overdose, or the effect of anesthetic and muscle relaxant drugs [10-16].

The main objectives of the mechanical ventilators are the maintenance of gaseous exchange, work relief respiratory muscles, reverse or avoid fatigue of the respiratory muscles, reduce the consumption of oxygen and allow the application of specific therapies. The main indications for starting the need for ventilation support are presented below in Table no. 1 [17-19].

Table No. 1: Normal and abnormal parameters, laboratory criteria for MV and initial ventilator settings.

Sr. No.	Parameters	Normal	Consider MV
1	Respiratory rate (bpm)	12-20	>35
2	Tidal Volume (ml/kg)	5-8	<5
3	Vital Capacity (ml/kg)	65-75	<50
4	Minute volume (L/min)	5-6	>10
5	Maximal inspiratory pressure (cmH_2O)	80-120	> 25
6	Maximal expiratory pressure (cmH_2O)	80-100	< 25
7	Dead space (%)	25-40	>60
8	$PaCO_2$ (mmHg)	35-45	>50
9	PaO_2 (mmHg) (FiO_2 = 0.21)	>75	<50
10	$P(A-a)O_2$ (FiO_2 = 1.0)	25-80	>350
11	PaO_2 /FiO_2	>300	<200
12	pH	7.35	< 7.32

* *FiO_2- fraction of inspired oxygen; mL/kg- milliliters per kilogram; L- liters; cmH_2O- centimeters of water; bpm- breaths per minute; PaO_2- partial pressure arterial oxygen; $PaCO_2$- partial pressure of carbon dioxide; pH- power of hydrogen.*

WORKING MECHANISM:

Mechanical ventilators usually require 3 basic components for their working:

1. Input Source.

2. Conversion and Control unit.

3. Output waveforms.

1. Input Sources: Mechanical ventilators are powered by electricity or compressed gases. Electricity is supplied either from wall outlets or from batteries to run the compressor of ventilators. Compressed gas is supplied from the tanks or from the hospital pipeline source supplying compressed air and oxygen at 50 psi (pounds per square inch). Mostly compressed gas generated ventilators are used in ICUs. The limiting parameters are time, pressure and volume responsible for determining specific rate of gas to be delivered to lungs [34, 65].

2. Conversion and Control unit:

To adjust the air drift into the patient's airway, primary control variables are pressure, flow, volume and time. Dual control mode is applicable in moderate to severe lung disease [8, 65].

i. Pressure-controlled ventilation: The ventilator maintains the same pressure waveform, in the mouth regardless of changes in lung characteristics. In this ventilation occur by either pressure control on body surface or airway portion. It delivers flow of air until the preset amount of airway pressure limit is reached and the valve opens to expel air. The volume of air to be delivered depends on the airway resistance and lung capacity [9, 35].

ii. Flow controlled ventilation: Ventilator volume delivery and volume waveform remain constant and are not affected by changes in lung characteristics. Flow is measured as;[34,65]

Flow= Volume/ Time

iii. Volume-controlled ventilation: Ventilator volume delivery and volume waveform remain constant and are not affected by changes in lung characteristics. It delivers flow of air into the patient's trachea until a pre-set volume of air is reached when the flow is stopped the chest recoils and the air is expelled out [9,35].

iv. Time controlled ventilation: Pressure, volume, and flow curves can change as lung characteristics change. Time remains constant [34,65].

v. Dual-controlled ventilation: These combine both the advantages of volume and pressure control and delivers airflow based on the requirement and response of the patient [9,35].

Volume controlled ventilation is the most recommended mode in patients with ARDS and other such comorbidities [35,38]. But few of them prioritize pressure controlled over volume controlled, depending on the variable conditions [35,39].

3. Output Waveforms:

As the study of cardiology requires the use of electrocardiogram and blood pressure waveforms, similarly mechanical ventilators requires knowledge of output waveforms. The output waveforms of interest indicate the levels of pressure and volume flow [34,35].

ROLE OF VENTILATORS IN COVID-19 PATIENTS' TREATMENT:

WHO revealed that about 80% of people suffering with COVID-19 recovered without any hospitalization. But one person in six becomes severely ill, required to be hospitalized dealing with poor cardio-respiratory functions. Fluids and mucus can block or drop down the oxygen levels in coronavirus infection, damaging the lungs and thereby making it difficult to breathe. To overcome the difficulty of breathing, mechanical ventilator act as a supportive device for COVID-19 patients. They push oxygen rich air into the lungs. It also acts as a humidifier as it adds heat and moisture to the supplied air. MV aid COVID-19 patients breathing until the immune system is not restored. The treatment can clear the infection and the proper lung functioning under rest [8, 9, 23, 33-35].

In China, among all confirmed COVID-19 cases admitted to the ICU, 45% required ventilation. Around 2,583 of 79,824 patients received intubation and IMV [7].

Challenging and careful dealing advised with adult and pediatric sufferers of COVID-19. Advancements and modifications can be done in ventilation therapies as per the patient's condition, age and sex, under guided protocols. Older victims have higher illness scores and more comorbidities like SARI, ARDS and/or respiratory failure, therefore hospitalization is essential [4, 7, 24]. Emergency oxygen supply in COVID-19 patients with SARI and related insufficiencies is to target SpO_2 in a range of 90-95%. Adults and children can be treated with intravenous fluids along with oxygenation if MV facilities are insufficient [24, 25]. Confirmed cases of COVID-19 with ARDS require advanced oxygen/ventilator support. Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires MV [24, 26]. In selected patients of hypoxemic respiratory failure, NIV along with high flow nasal oxygenation is recommended. Usually lower tidal volumes (4–8 mL/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cmH2O) are implemented in MV [26, 28]. Patient may require deep sedation prior ventilation if diagnosed with sepsis induced respiratory failure [26, 28]. Very few pediatrics and mostly adult COVID-19 patients with severe ARDS can be prone ventilated for 12-16 hours per day [26, 29]. In order to minimize the duration of ventilation, in some patients, conservative fluid management strategy can be selected [24, 26].In patients with moderate or severe ARDS, during lung protective ventilation, higher PEEP (positive end-expiratory pressure) is suggested based on the FiO_2 required to maintain SpO_2. Need of initiation of oxygen therapy and intubation is summarized in Fig 2 [24, 31].

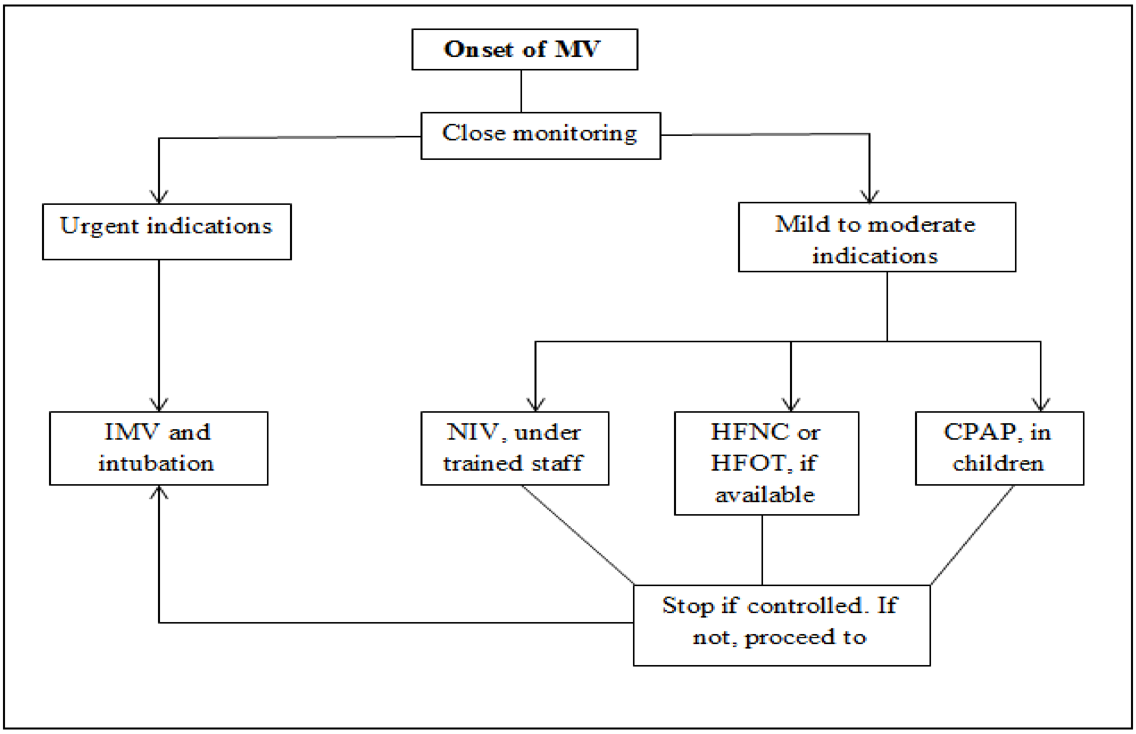

Figure No. 2: Conditions of initiation of mechanical ventilation (MV)

***IMV: Invasive Mechanical Ventilation; NIV: Noninvasive Ventilation; HFNC: High Flow Nasal Cannula; HFOT: High Flow Oxygen Therapy; CPAP: Continuous Positive Airway Pressure*.**

ASSOCIATED RISKS:

In an early outbreak of pandemic in China, around 97% COVID-19 patients on IMV died. 53% died due to respiratory failure, 7% from shock, 33% from both, and 7% with unclear mechanisms. Among them, older patients (60 years and above) had maximum deaths. [58-60]. An investigation on COVID-19 positive cases on IMV is shown below in Fig 3. It covered 333 hospitals with overall mortality rates in between 48-54% [42].

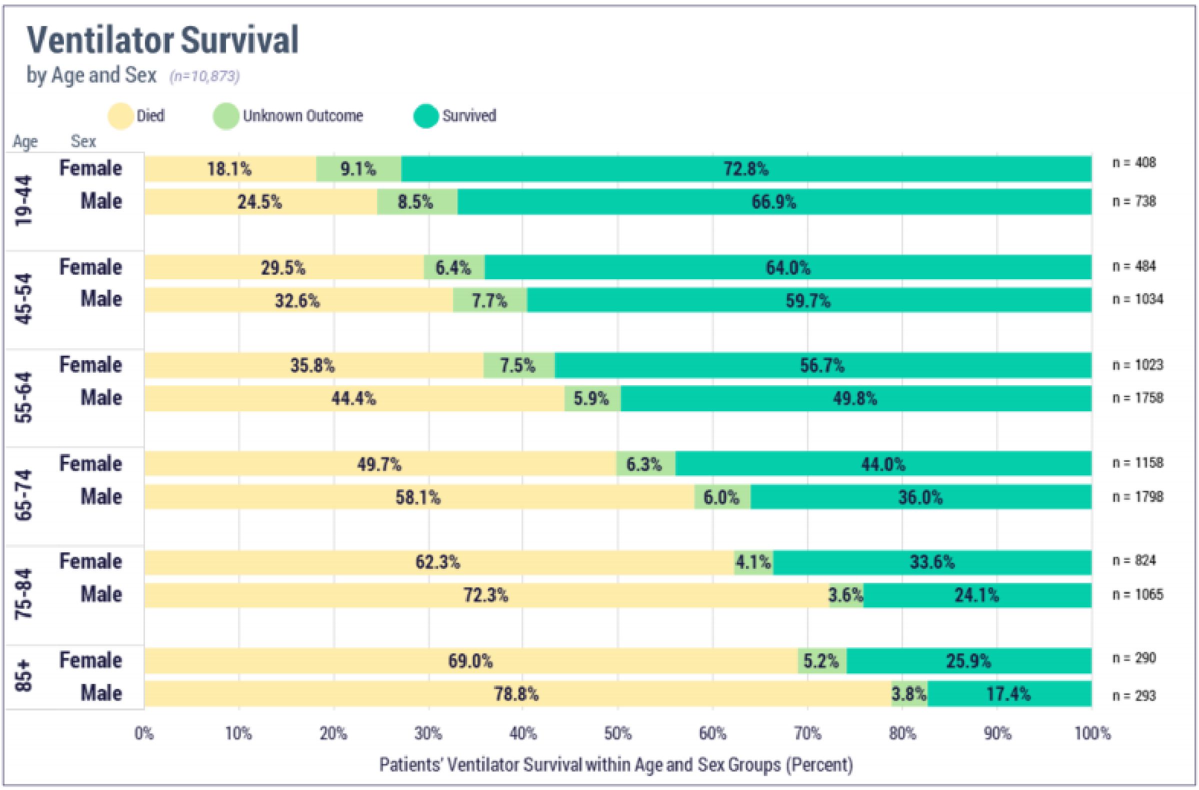

Figure No. 3: Mortality data of 42 million COVID-19 patients received IMV.

Not preferably all the time, but intubation offers several other problems to the patients under MV. 9.5% COVID-19 patients on MV were observed with acute lung injury and 43.5% with hyperoxemia. Supply of liberal oxygen, unregulated pressure and leaking ventilators may directly harm the lungs. In the starting 24 hours if high FiO_2 with low or high PaO_2 levels delivered may increase mortality rates in MV. Use of low tidal volume in MV in patients with ARDS has a positive effect on mortality and ventilator-free days. Generally, improperly calibrated equipment and inadequate trained staff may cause negative impact on critically ill patients requiring long term ventilation mode [24, 35-37].

HFOT (High Flow Oxygen Therapy) or HFNC (High Flow Nasal Cannula) and leaking NIV interfaces may generate contaminated aerosols. Nosocomial transmission of any microbe is also likely to occur from NIV. Moreover, it should be evaded on hemodynamic instable, multi-organ failure, or an abnormal mental status patient. IMV is recommended in this state. Initially, HFNC and NIV were extensively used in China despite awareness of illness level of COVID-19 patients. In ARDS patients' insufficient pre-oxygenation before intubation may lead to fatalities [24, 41, 61, 62].

During prolonged IMV and intubation, infectious bacteria may enter causing ventilator-associated pneumonia and venous thromboembolism. Other incidences like catheter-related bloodstream infection, pressure and stress ulcers and gastrointestinal bleeding may also occur. In moderate or severe ARDS conditions, PEEP titration associated risks are end-inspiratory over distension eliciting to lung injury and higher pulmonary vascular resistance. Under guided protocol monitoring, prior trails of CPAP in children and NIV or IMV in adults may decrease such risky accidents [24, 30].

WORLDWIDE MANAGEMENT AND AVAILABILITY:

Various attempts are going on worldwide to increase the availability and efficiency for use of ventilators in COVID-19 treatment. Majorly most of the countries are struggling with a lack of capacity, resources and resolve. Health centers are already reporting shortage of key equipments needed for critical care, neonatal care, emergency care and others. Demand of ventilator is a prime device essential to treat severe cases of COVID-19. It is used to manage breath and ample air supply in the affected patients. Due to which concentration on its proper application and availability is main question [1, 7]. Concerning over it, production increased from 30-50%. About 77,000 new ventilators required to meet global demand in 2019. In April 2020, around 30,000 additional ventilators were wielded in New York City itself. Significant contributors are pushing for the development and distribution of as many ventilators as possible around the world. Four major medical ventilator market regions are Americas, Asia Pacific, Europe, and the Middle East & Africa. The leading participants in the medical ventilator market are Koninklijke Philips N.V. (the Netherlands), Medtronic (Ireland), ResMed (U.S.), General Electric Company (U.S.), Becton, Dickinson, and Company (U.S.), Allied Healthcare Products Inc. (U.S), Hamilton Medical (Switzerland), Teleflex Incorporated (U.S.) [53].

At Jet Propulsion Laboratory (JPL), South California of NASA, special ventilator, named VITAL (Ventilator Intervention Technology Accessible Locally) was developed. After receiving approval from USFDA on April 30, 2020, these ventilators are widely used in hospitals for severe COVID-19 patients [48].

E-VITS (Emergency Ventilator in Institute of Technology and Science) is a prototype of a simple and low-cost mechanical ventilator developed by the Department of Physics Engineering, ITS, Surabaya. The first version of the E-VITS prototype was launched on April

7, 2020 at ITS Robotics Building. After that, the team continues to develop to achieve the standardization from Health Facilities Safety Center (BPFK) Surabaya. Dr. Aulia mentioned that the five standards required by BPFK are electrical safety test, visual test, endurance test, performance test, and the availability of documentation related to the technical, operational, and maintenance of the ventilator. Therefore, the team made a thorough internal test to ensure that E-VITS meets all five requirement aspects [51].

Philips is a major manufacturer of mechanical ventilators. The R&D team modified Philips Respironics to Philips Respironics E30, an emergency use ventilator during COVID-19 pandemic. It is used in IMV as well as NIV and after use they may be disposed or returned to the company [50].

INDIAN PERSPECTIVE:

As figured, the numbers of COVID-19 positive cases are increasing with date; around 767,296 confirmed cases are there in India [52]. On account of this, on April 9, about 49,000 ventilators were ordered by government of India. Following it, on May 14, an official package of 2000 crores amount was put forth for purchase of 50,000 additional "Made in India" ventilators. Average price of a ventilator is 8-10 lakh [54, 55]. Under a mutual partnership, President of America also promised to donate ventilators [49, 54]. According to the Ministry of Health and Family Welfare, India has 18,855 ventilators available for COVID-19 patients which would be insufficient in upcoming days. In an information by the government's empower group about 60,000 more ventilators had been booked. On May 15, Dr. Harsh Vardhan, Health and Family Welfare Minister, expected about 0.45% of the COVID-19 patients in India were on ventilator which is expected to increase [57].

On May 28 Indian Institute of Technology, Mandi developed a low cost (around Rs 4,000) smart mechanical ventilators. Breath rate and volume of air circulating in the patient's lungs can be controlled through a mobile application. The research team also invented a low cost (under Rs 25,000) self-inflating bag electric motor operated mechanical ventilator. This self-inflation bag can blow the oxygen into the patient's lungs either through invasive or noninvasive mode [56].

The three Indian companies- Alpha Design Technologies Pvt Ltd., Bharat Forge Ltd. and Medha Servo Drives Pvt Ltd. got licenses from National Aeronautics and Space Administration (NASA) to manufacture its indigenously ventilators for critical COVID-19 patients. 18 other companies, including eight American and three Brazilian, have been selected to manufacture the critical breathing devices [48].

FUTURE INSIGHTS:

However, some countries are claiming to soon release vaccines and other medications for COVID-19, but it is a time taking process. Till then to manage the severity of pandemic, alternate available resources are required to be utilized wisely. On a large scale, there must be a complex mass collaboration of medical departments with private and government agencies. It would produce more strategic framework and sequential planning in pre-existing deformity or disease if any. Moreover, the corporation may open new horizons with for producing rapidly effective, cheap and ready to use ventilators specially designed for such viral infections in future. Opting recent advances in the field of science and technology, rationale use of ventilators may decrease the adversity and death rates.

Figure No. 4: Adult COVID-19 patient on ventilator.

Countries like US, Russia, India and many others are at their peak of new positive COVID-19 cases daily. Therefore a broad range of estimates of the number of ventilators will be needed to care in critical scenarios. Especially in low and middle income countries, MV requirement will increase with the span of pandemic [64]. Experts suggested that by 2023, the market size of ventilators will grow at a CAGR (Compound Annual Growth Rate) of 7.9%. Alone US may invest more than $2.5 billion in ventilators manufacturing. Soon there will be worldwide tremendous need for MV [53].

To compensate the shortage of mechanical ventilators, American Hospital Association is planning to introduce hospital-led ventilator exchange program. An objective is to provide 60,000 unused ventilators to COVID-19 hot spot hospitals. The US government appealed automotive companies to come forward in manufacturing and supply of ventilators. Concerning this, Tesla (a renowned automotive company), has joined hands with medical device companies. Philips promised to deliver 43,000 ventilators for COVID-19 patients by the end of 2020. General Motors also have a contract with government to manufacture 30,000 more ventilators till August [53].

French government outlaid to introduce $38 million fund for this pandemic. Out of which around $4.4 billion fund will be utilized to purchase masks and ventilators. The medical gas specialists Air Liquide SA and Peugeot SA, Schneider Electric SE and Valeo SA joined the consortium. This partnership indicated to manufacture and supply about 10,000 ventilators in the region. Public Assistance Hospital in Cochin produced 60 3D printers to manufacture valves for emergency artificial ventilators in huge quantities. This can meet the demand of ventilators during this COVID-19 pandemic [53].

In India, the Union Government ordered the procurement of 40,000 new ventilators. The Governments of India have requested various automotive companies to help in the development and distribution of medical ventilators across the world. Indian companies such as Maruti, Mahindra, and Tata Motors have increased the development and distribution of ventilators across the world [53].

CONCLUSION:

The dominance of ventilators in the treatment line is concerned on two main factors. Primarily the successful cure of COVID-19 patients and secondarily the protection of healthcare providers from viral transmission tasked to perform intubation and ventilation. In an alignment, therapeutic directions should be strictly followed as recommended by researchers. Tailored approaches can be employed for COVID-19 patients with comorbidities like ARDS, heart failure and other associated deformities. Conditions may vary among different age groups, sexes and pregnant patients.

Under supervision, MV improved longevity of infected cases by monitoring respiratory rates. Both IMV and NIV played equally important roles. CPAP in children and HFNC in adults are practiced continuously due to potential outputs in curbing the disease. However, risk assessment studies are on verge to prevent ventilation related tragedies.

International efforts of all communities on sweeping the pandemic are creditable. It is supposed that the economic support, collaborations and contracts among authorities would somehow improve the health of sufferers. The struggle of researchers and hospitals crew cannot be ignored. Although the global impact of it is yet uncertain, readers are urged to update themselves regularly.

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