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OPINIONS AND ORDERS

REHEARING ORDER

OTHER DOCUMENTS

OPINION, UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT (JUNE 28, 2023)

Note: This disposition is nonprecedential

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

FLEUR TEHRANI,

Appellant,

v.

HAMILTON TECHNOLOGIES LLC,

Appellee.

No. 2022-1732

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2020-01199.

Decided: June 28, 2023

Before: REYNA, STOLL, and STARK, Circuit Judges.

STARK, Circuit Judge.

Dr. Fleur Tehrani invented and owns U.S. Patent No. 7,802,571 (the "'571 patent"). Hamilton Technologies LLC ("Hamilton"), a licensee of another of Dr. Tehrani's patents, petitioned for inter partes review ("IPR") of the '571 patent. The Patent and Trial

Appeal Board ("Board") instituted an IPR and ultimately concluded that claims 1-6, 9-12, 29-33, and 41 of the '571 patent were invalid as obvious. *Hamilton Techs. LLC v. Tehrani*, IPR2020-01199, 2021 WL 6339598 (P.T.A.B. 2021), J.A. 1-69. Dr. Tehrani sought Director review, which was denied. She then timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A). We affirm.

I

The '571 patent, entitled "Method and Apparatus for Controlling a Ventilator," relates to "a method and apparatus for controlling a ventilator based on the measured levels of oxygen of the patient on the ventilator, as well as other physical conditions of the patient." '571 patent 1:20-23. The method and apparatus includes a "first means" comprising "a programmable microprocessor" controlled by "a software algorithm" that operates on input data, such as respiratory mechanics, pressure-volume data, and the patient's measured carbon dioxide levels, to provide "digital output data to control the ventilator and the gas mixer of the ventilator." *Id.* at 2:43-54. The software algorithm includes a proportional, integral, derivative ("PID") control program which "is designed to automatically adjust" the fraction of inspired oxygen in a patient's inspiratory gas ("FIO2") and the patient's Positive End-Expiratory Pressure ("PEEP") "based on at least the measured oxygen levels of the patient." *Id.* at 2:54-57. "The processing means detects hazardous conditions based on the input data and/or artifacts, replaces and/or corrects the measurement artifacts, and instructs generation of appropriate warning signals." *Id.* at

2:60-63. The subsequent output data is then transmitted through the second means "to a Signal Generator which is equipped with converters and/or other electronic components to generate the control and appropriate warning signals," which are then supplied to the ventilator or a mixer regulator unit to adjust the concentration of oxygen. *Id*. at 3:5-17.

Figures 3a-i of the '571 patent show a flowchart describing the software algorithm's process. The first loop begins after establishing initial values of FIO2 and PEEP, desired set points for arterial partial pressure of oxygen, threshold values for arterial hemoglobin oxygen saturation ("SpO2"), and a loop indicator. *Id*. at 7:47-8:25. The patient's SpO2 data is input and used to calculate the arterial partial pressure of oxygen, which is then compared to a minimum acceptable value. *Id*. at 8:26-44. If the value is greater than or equal to the minimum acceptable value, the value is accepted; otherwise, an alarm is generated. *Id*. at 8:45-52. The subsequent steps control FIO2, either with a rapid stepwise control scheme for fast declines in SpO2 or a finely controlled PID algorithm. *Id*. at 10:16-23. After FIO2 is determined, the protocol then calculates the ratio of PEEP/FIO2. *Id*. at 10:43-45. If the ratio is not within a clinically acceptable range, the PEEP is increased or decreased by a fixed increment over a fixed period, followed by observation and measure of any change in PEEP on the patient's oxygenation. *Id*. at 11:48-60.

Of the challenged claims, claims 1 and 29 are independent. Claim 1, which is directed to an apparatus, is illustrative and reproduced below:

> 1. An apparatus for automatically controlling a ventilator comprising:

> first means for processing data indicative of at least a measured oxygen level of a patient, and for providing output data indicative of: required concentration of oxygen in inspiratory gas of the patient (FIO2) and positive end-expiratory pressure (PEEP) for a next breath of the patient;
>
> wherein FIO2 is determined to reduce the difference between the measured oxygen level of the patient and a desired value;
>
> wherein PEEP is determined to keep a ratio of PEEP/FIO2 within a prescribed range and, while keeping the ratio within the prescribed range, to keep the measured oxygen level of the patient above a predefined value; and
>
> second means, operatively coupled to the first means, for providing control signals, based on the output data provided by the first means, to the ventilator;
>
> wherein the control signals provided to the ventilator automatically control PEEP, and FIO2, for a next breath of the patient.

Id. at 12:49-13:3. Claim 29 is directed to a method for automatically controlling a ventilator with steps like those recited in claim 1. *Id*. at 15:15-31.

II

The Board concluded that the claims were invalid as obvious on two grounds: (1) a combination of Carmichael, Anderson, Dr. Tehrani's U.S. Patent No. 4,986,268 (the "'268 patent"), and Rossi,[1] and (2) a combination of Taube, Carmichael, ARDSNET, Clemmer, and Rossi.[2]

Dr. Tehrani raises a dozen issues on appeal. None has merit and only a few warrant discussion.

Dr. Tehrani argues that the Board should not have credited Hamilton's expert, Dr. Richard Imbruce, because he is "a) not a respiratory therapist, b) none of his listed patents [are] on mechanical ventilation, and c) he was disqualified in another case for offering expert testimony on a subject he was not familiar with." Appellant's Br. at 34. Dr. Tehrani also claims that Dr. Imbruce is not a person having ordinary skill in the art. *Id.* at 35. We review the Board's determinations as to what weight to accord expert testimony for abuse of discretion. *See Shoes by Firebug LLC v.*

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[1] Laurence C. Carmichael et al., Diagnosis and Therapy of Acute Respiratory Distress Syndrome in Adults: An International Survey, 11 J. Critical Care 9 (March 1996) ("Carmichael"); Jeffrey R. Anderson & Thomas D. East., A Closed-Loop Controller for Mechanical Ventilation of Patients with ARDS, 38 Biomedical Scis. Instrumentation Symposium 289 (2002) ("Anderson"); A. Rossi, Intrinsic Positive End-Expiratory Pressure (PEEPi), 21 Intensive Care Med. 522 (1995) ("Rossi").

[2] U.S. Patent No. 5,388,575 ("Taube"); The Acute Respiratory Distress Syndrome Network, Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Lung Respiratory Distress Syndrome, 342 New England J. Med. 1301 (2020) ("ARDSNET"); U.S. Patent No. 6,148,814 ("Clemmer").

Stride Rite Children's Grp., LLC, 962 F.3d 1362, 1372 (Fed. Cir. 2020).

The Board did not abuse its discretion. As the Board explained, Dr. Imbruce has decades of experience with ventilator devices and portable oxygen generators, including developing clinical protocols for new modalities in artificial ventilation and oxygen delivery therapies for hemorrhagic shock in wounded soldiers. Dr. Imbruce is an inventor on two patents related to a portable oxygen generator for emergency use, has worked in industry related to oxygen delivery and artificial ventilation since 1981, and has at least eleven years of clinical experience in pulmonary function and respiratory therapy. The Board found Dr. Imbruce's testimony "adequate," J.A. 14, and it was free to do so.

Dr. Imbruce is a person of ordinary skill in the art, as he is a "clinician specializing in treating respiratory failure issues with at least five years of practical clinical ventilator experience treating such conditions," which is one of the disjunctive options provided in the agreed-upon definition of an ordinary artisan, which the Board adopted. J.A. 13. Even assuming there was error in the Board failing to expressly find that Dr. Imbruce was a person of ordinary skill in the art, such error was harmless, because, as we have explained, Dr. Imbruce plainly has the qualifications to make him such a person.[3]

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[3] At oral argument, Dr. Tehrani's counsel emphasized that Dr. Imbruce's clinical experience occurred more than 40 years ago. Oral Arg. at 9:44-10:29. The Board's definition of a person of ordinary skill in the art imposes no restriction as to when the skilled artisan's clinical experience must have occurred. Issues

Dr. Tehrani also contends that the Board should have construed the claim term "for a next breath of the patient" as controlling PEEP and FIO2 for "a patient's breath immediately following in time" or "the next breathing cycle of the patient." J.A. 35-36 n.11; Appellant's Br. at 41-43. Hamilton instead proposed the plain and ordinary meaning as not limited to the immediate next breath or breathing cycle. J.A. 2509-11. "[W]e review the Board's ultimate claim constructions *de novo*." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1297 (Fed. Cir. 2015), overruled on other grounds by *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017). Here, however, the Board did not actually construe this claim term. Instead, after noting that Dr. Tehrani's proposed construction would contradict her argument that the specification requires adjusting PEEP after a 240-second delay, *see* '571 patent 11:56-60, the Board determined that the claim limitation was taught in the prior art combinations "regardless of whether we adopt Patent Owner's or Petitioner's claim construction." J.A. 35-36 n.11. The Board had substantial evidence for this finding. *See, e.g.*, J.A. 1114-15, 1118 (Anderson stating "[t]he computer constantly reads important [input] information" to "continuously control[] FiO2 and PEEP" and disclosing graph showing changes in FIO2 and PEEP over time); J.A. 446 ('268 patent teaching "controlling a respirator" based on input data and "provid[ing] digital output data representing the

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relating to the extent and timing of Dr. Imbruce's clinical experience may affect the weight that the Board should choose to give his opinions, but those issues do not render his opinions unreliable. There is no basis for us to find the Board abused its discretion in the weight it placed on this witness' testimony.

amount and optimum frequency of ventilation required for the next breath"). In combination, the prior art teaches that FIO2 and PEEP can be controlled for an immediate next breath or a later breath, satisfying both parties' competing constructions.

Most of Dr. Tehrani's remaining arguments challenge the Board's factual findings, which we review for substantial evidence. "Obviousness under 35 U.S.C. § 103 is a mixed question of law and fact. We review the Board's ultimate obviousness determination de novo and underlying fact-findings for substantial evidence." *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). Two examples are sufficient to illustrate the lack of merit in Dr. Tehrani's contentions on appeal.

Dr. Tehrani argues that Anderson's use of look up tables contradicts the '571 patent's PID control and, further, that Carmichael does not teach the use of an automatic ventilator and a ratio of PEEP/FIO2. Oral Arg. at 5:06-7:18, 7:48-8:57. Substantial evidence supports the Board's finding that "it would have been obvious to employ Anderson's automated system to implement Carmichael's treatment protocol for adjustment of PEEP and FIO2 in ARDS [(Acute Respiratory Distress Syndrome)] patients." J.A. 37. As Dr. Imbruce explained, the combination of Anderson and Carmichael, along with the '268 patent and Rossi, teaches every challenged limitation of the '571 patent. In particular, Anderson teaches a "closed-loop control system," using an oxygenation sensor and computer to use a "traditional proportional-integral-derivative (PID) approach" to "continuously control[] FIO2 and PEEP settings on a Hamilton Amadeus ventilator." J.A. 1114. Substantial evidence, including Dr. Imbruce's

second declaration, also supports the Board's finding that Anderson's look-up tables "contain the logic used to dictate if changes in therapy are needed 'based on the patient's current level of PaO2 and current PEEP and [FIO2] settings.'" J.A. 30 (quoting J.A. 1116 (Anderson)). Anderson uses "[FIO2] and PEEP PID controllers that calculate the amount of therapy adjustment." J.A. 1116. Anderson's look-up tables serve the same function as the '571 patent's loop indicators, defining the logic that determines if and when PID controllers change FIO2 and PEEP. J.A. 31, 2715; '571 patent 8:23-25.

The Board also had substantial evidence to conclude that Carmichael teaches a treatment protocol of increasing FIO2 and incrementally changing PEEP and using the relationship between FIO2 and PEEP to achieve the desired oxygen saturation level within a prescribed range, as depicted below in Carmichael's Figure 7. J.A. 26-27, 29, 422 (illustrating maximum acceptable PEEP used at each FIO2 level); *see also* J.A. 215-17 ("Carmichael discloses a desired oxygen level of a patient 'should be achieved through the use of increased [FIO2] and incremental application of PEEP.") (quoting J.A. 423-24). The slope in Figure 7 indicates the limits of the relationship between FIO2 and PEEP. See Oral Arg. at 14:30-16:19; *see also* J.A. 29 ("Figure 7 of Carmichael shows that the maximum level of acceptable PEEP increased as the FIO2 level increased.").

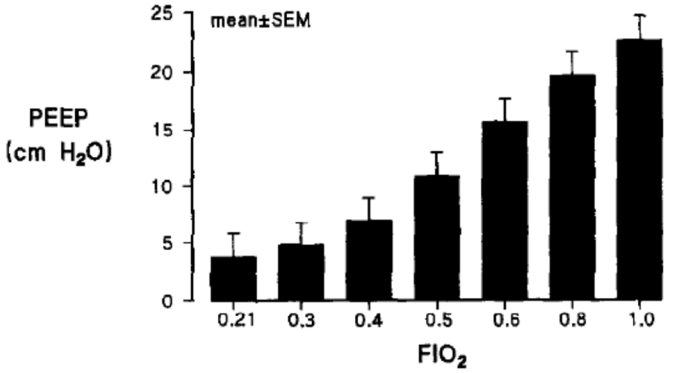

Fig 7. The maximum PEEP used at various FIO_2s.

J.A. 422 (Carmichael Fig. 7).

Many of Dr. Tehrani's arguments are directed to pointing out limitations that are not present in individual prior art references, but what matters is what the combination of references collectively contain, not what they individually contain or lack. *See Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1380 (Fed. Cir. 2023) (explaining courts "'look to interrelated teachings of multiple patents'") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)). Identifying flaws in individual references does not defeat Hamilton's showing that both combinations relied on by the Board disclose, collectively, all the limitations of the challenged claims.

III

We have considered Dr. Tehrani's remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm.

AFFIRMED

JUDGMENT, FINAL WRITTEN DECISION U.S. PATENT AND TRADEMARK OFFICE (DECEMBER 28, 2021)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HAMILTON TECHNOLOGIES LLC,

Petitioner,

v.

FLEUR TEHRANI,

Patent Owner.

IPR2020-01199
Patent 7,802,571 B2

Before: Josiah C. COCKS, Kevin W. CHERRY, and Jamie T. WISZ, Administrative Patent Judges.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Denying-In-Part, Granting-In-Part, and Dismissing-In-Part Petitioner's Motion to Exclude

Denying-In-Part and Dismissing-In-Part Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

CHERRY, Administrative Patent Judge.

I. Introduction

A. Background and Summary

Hamilton Technologies LLC ("Petitioner") filed a Petition (Paper 2, "Pet.") seeking *inter partes* review of claims 1-6, 9-12, 29-33, and 41 of U.S. Patent No. 7,802,571 B2 (Ex. 1001, "the '571 patent"). Petitioner supported the Petition with the Declaration of Richard Imbruce. Ex. 1002. Fleur Tehrani ("Patent Owner") filed a Preliminary Response. Paper 5 ("Prelim. Resp.").

On January 6, 2021, based on the record before us at the time, we instituted an *inter partes* review of all challenged claims on all grounds alleged. Paper 6 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Request for Rehearing of our Institution Decision. Paper 9. We denied Patent Owner's Request for Rehearing on March 5, 2021. Paper 17 ("Reh'g Dec.").

Patent Owner filed a Response in opposition to the Petition (Paper 19, "PO Resp."). Petitioner filed a Reply in support of the Petition (Paper 25, "Reply"). Patent Owner also filed a Sur-Reply in response to Petitioner's Reply. Paper 28 ("Sur-Reply").

Petitioner filed a motion to exclude evidence. Paper 35 ("Pet. Mot."). Patent Owner filed an opposition. Paper 37 ("PO Opp."). Petitioner filed a Reply. Paper 40 ("Pet. Mot. Reply"). Patent Owner also filed

a motion to exclude evidence. Paper 33 ("PO Mot."). Petitioner filed an opposition. Paper 37 ("Pet. Opp."). Patent Owner filed a reply. Paper 41 ("PO Mot. Reply").

Both parties requested an Oral Hearing. *See* Paper 32. A transcript of the Oral Hearing is entered in the record. Paper 53 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. The evidentiary standard is a preponderance of the evidence. *See* 35 U.S.C. § 316(e) (2018); 37 C.F.R. § 42.1(d) (2020). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

B. Real Parties in Interest

Hamilton Technologies LLC identifies itself and its affiliated subsidiaries, including Hamilton Holding Medical Corporation, Hamilton Company, Hamilton Medical AG, Hamilton Medial Inc., and Hamilton Bonaduz AG, as the real parties in interest. Pet. 1. Dr. Fleur T. Tehrani, Ph.D., P.E., identifies herself as the real party in interest. Paper 4, 1.

C. Related Matters

Petitioner identifies that GB 2 423 721 B, which claims priority to the '571 patent, is the subject of an ongoing UK civil action: *Fleur Tehrani v. Hamilton Bonaduz AG et al.*, High Court of Justice, Business and Property Courts of England and Wales, Intellectual Property List (ChD), Intellectual Property Enterprise Court, Claim IP-2019-000196, Issue date 29 November 2019. Pet. 1. Patent Owner also lists the ongoing UK litigation, and states that there are no

related judicial or administrative matters in the U.S. Paper 4, 1.

D. The '571 Patent

The '571 patent, titled "Method and Apparatus For Controlling a Ventilator," issued September 28, 2010, from U.S. Application No. 10/935,446, filed September 7, 2004, and claims the benefit of priority to U.S. Provisional Application No. 60/481,693, filed November 21, 2003. Ex. 1001, (54), (45), (21), (22), (60). The '571 patent relates to "a method and apparatus for controlling a ventilator based on the measured levels of oxygen of the patient on the ventilator, as well as other physical conditions of the patient." *See id.* at 1:20–23. Specifically, the '571 patent describes a method and apparatus to control Positive End-Expiratory Pressure ("PEEP") and the concentration of oxygen in a patient's inspiratory gas, or the fraction of inspired gas ("FIO2" or "FIO2") to improve the oxygenation of patients during ventilator therapy. *Id.* at 2:25-27, 3:52-59.

We reproduce Figure 1 from the '571 patent below.

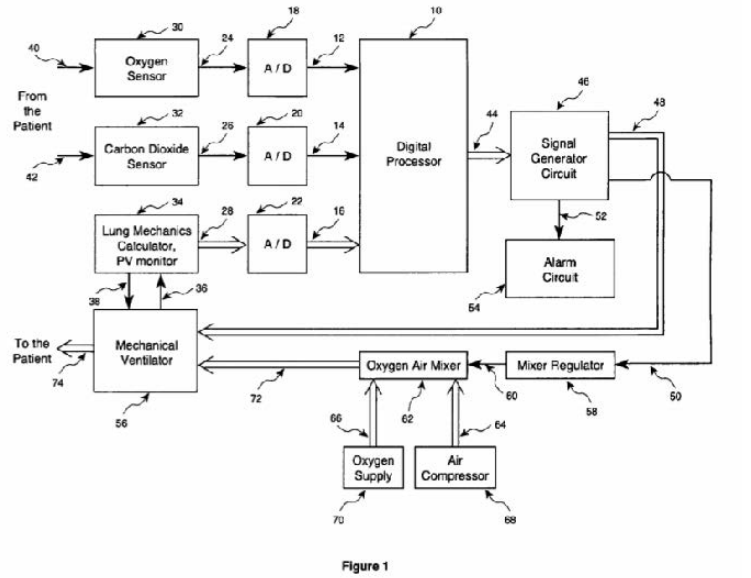

Figure 1

Figure 1 depicts a block diagram of a mechanical ventilator and the control apparatus of the claimed invention. Ex. 1001, 3:26–28. Digital processor 10 includes a programmable controller coupled to receive outputs 12, 14, and 16 of A/D converters 18, 20, and 22. *Id.* at 3:67-4:2. The A/D converters receive inputs 24, 26, and 28 from oxygen sensor 30, carbon dioxide sensor 32, and lung mechanics calculator and PV monitor 34. *Id.* at 4:5-9. Inputs 40 and 42 for sensors 30 and 32 come from the patient, and input 36 for monitor 34 comes from mechanical ventilator 56. *Id.* at 4:16-18, 22-24. Outputs 44 from digital processor 10 are applied to signal generator circuit 46. Signal generator circuit 46 sends alarm instruction signals 52 to alarm circuit 54, control signals 48 to mechanical ventilator 56, and control signals 50 to mixer regulator

circuit 58.[1] *Id.* at 4:26-36. Control signals 48 include signals to control PEEP, breathing frequency, tidal volume, and adjustment of the I:E ratio of the patient. *Id.* at 4:32-34. Control signals 50 include signals to control mixer 62 to adjust FIO2. *Id.* at 4:34-36.

The '571 patent describes that digital processor 10 has a software algorithm that automatically controls PEEP and FIO2 according to the method shown in the flow chart of Figures 3*a*-3*i*. *Id.* at 7:34-41. The desired set point for arterial partial pressure of oxygen is defined and the initial values of FIO2 and PEEP are set. *Id.* at 7:47-53, Fig. 3*a*, steps 200, 202, 204. Then, a time parameter (*e.g.*, TP) for PEEP adjustment is defined and initially set to zero and another parameter, AP, for PEEP adjustment is defined to control whether PEEP is controlled manually or automatically. *Id.* at 8:4-14, Fig. 3*a*, steps 206, 208. In the next step, threshold values for arterial hemoglobin oxygen saturation (SpO2) are defined for the specific patient. *Id.* at 8:15-17, Fig. 3*a*, step 210. A loop indicator is defined and a first loop is started. *Id.* at 8:23-25, Fig. 3*a*, step 212. The patient's SpO2 data is read from one of the input ports, and the arterial partial pressure of oxygen is calculated from the SpO2 data. *Id.* at 8:26-41, Fig. 3*a*, steps 214, 216. The calculated partial pressure of oxygen, PaO2, is compared with a minimum acceptable value to detect artifacts in the measurement of SpO2. *Id.* at 8:42-45, Fig. 3*b*, step 218. If the calculated PaO2 is found to be less than the minimum acceptable value, then an artifact is assumed,

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[1] A schematic diagram of signal generator circuit 46 and alarm circuit 54 for use in the invention is shown in Figure 4 of the '571 patent. Ex. 1001, 3:38-40, 12:4-22.

an alarm is generated, the SpO2 data is discarded and the previous value of PaO2 in memory is resumed. *Id.* at 8:45-49, Fig. 3*b*, steps 220, 222. If the calculated PaO2 is found to be greater than or equal to the minimum acceptable value, its value is accepted. *Id.* at 8:50-52.

In the next steps, FIO2 is automatically controlled. Ex. 1001, 8:53-10:15, Figs. 3*c*-3*e*. The '571 patent describes this process of automatic control of FIO2 as using two different mechanisms: (1) a rapid stepwise control scheme[2] which responds instantly to fast declines in SpO2, and (2) a more finely controlled PID algorithm[3] that provides fine control of FIO2 in the absence of sharp hazardous declines in SpO2. *Id.* at 10:16-23. The stepwise controller has three loops, each with its defined minimum and maximum SpO2 threshold levels. *Id.* at 10:23-26. The controller switches from PID control to the rapid stepwise algorithm only if rapid declines in SpO2 are detected. *Id.* at 10:28-30. Once in the stepwise mode, the controller continuously checks SpO2, and if it rises, the controller reduces FIO2 to minimize the exposure of the patient to high and toxic levels of FIO2. *Id.* at 10:30-33.

After the required FIO2 is determined, the procedure of adjusting PEEP begins with calculating the ratio of PEEP/FIO2. Ex. 1001, 10:43-45, Fig. 3*g*, step 282. If the control parameter AP was set for automatic

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[2] The rapid stepwise control scheme is shown in Figures 3*c*-3*e* and described in the '571 patent in column 8, line 53 through column 9, line 33.

[3] The PID control algorithm is shown in Figure 3*f* and described in the '571 patent in column 9, line 33 through column 10, line 15.

control of PEEP, then an automatic PEEP adjustment control loop is started. *Id.* at 10:61-64, Fig. 3*g*, step 284, Fig. 3*h*, step 294.

In performing the automatic PEEP adjustments, the PEEP/FIO2 value is kept within a clinically acceptable range. Ex. 1001, 11:48-49. If the PEEP/FIO2 value is too low, PEEP is increased by a fixed increment (*e.g.*, 2 cm H2O). *Id.* at 11:50-51, 10:64-11:18, Fig. 3*h*, steps 296, 298, 300, 302, Fig. 3*i*, steps 304, 306. If the PEEP/FIO2 value is within the acceptable range and SpO2 is low, then PEEP is increased by a fixed increment (*e.g.*, 2 cm H2O) to improve patient's oxygenation. *Id.* at 11:51-54, 11:37-47, Fig. 3*i*, step 320. On the other hand, if the PEEP/FIO2 value increases beyond a maximum defined value, the program reduces PEEP in fixed amounts (*e.g.*, 2 cm H2O). *Id.* at 11:54-56, 11:19-34, Fig. 3*i*, steps 308, 310, 312, 314, 316. In any case, the interval between two successive PEEP adjustments is at least equal to a fixed period (*e.g.*, 240 seconds), to allow for the changes in PEEP to have an observable and measurable impact on the patient's oxygenation. *Id.* at 11:56-60.

E. Illustrative Claims

The Petition challenges claims 1-6, 9-12, 29-33, and 41. Of these, claims 1 and 29 are independent. Claim 1, which is illustrative of the subject matter at issue, is directed to an apparatus and is reproduced below.

1. An apparatus for automatically controlling a ventilator comprising:

first means for processing data indicative of at least a measured oxygen level of a patient, and for providing output data indicative of:

required concentration of oxygen in inspiratory gas of the patient (FIO2) and positive end-expiratory pressure (PEEP) for a next breath of the patient;

wherein FIO2 is determined to reduce the difference between the measured oxygen level of the patient and a desired value;

wherein PEEP is determined to keep a ratio of PEEP/FIO2 within a prescribed range and, while keeping the ratio within the prescribed range, to keep the measured oxygen level of the patient above a predefined value; and

second means, operatively coupled to the first means, for providing control signals, based on the output data provided by the first means, to the ventilator;

wherein the control signals provided to the ventilator automatically control PEEP, and FIO2, for a next breath of the patient.

Ex. 1001, 12:49-13:3. Independent claim 29 is directed to a method for automatically controlling a ventilator comprising steps similar to the functions recited in claim 1. *Id.* at 15:15-31.

F. Evidence

The following references form the basis of the grounds presented in the Petition:

References	Date	Exhibit No.
Carmichael, L.C. et al., "Diagnosis and Therapy of Acute Respiratory Distress Syndrome in Adults: An International Survey," J. of Critical Care, Vol. 11, No. 1 (March 1996), pp. 9–18 ("Carmichael")	March, 1996	1004
US 5,388,575 ("Taube")	Feb. 14, 1995	1005
US 4,986,268 ("Tehrani '268")	Jan. 22, 1991	1006
Brower, R.G., M.D. et al., "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," The New England J. of Med., Vol. 342, No. 18 (May 4, 2000), pp. 1301–08 ("ARDSNET").	May 4, 2000	1007
US 6,148,814 ("Clemmer")	Nov. 21, 2000	1008

Waisel, D.B. et al., "PEFIOS: An Expert Closed-Loop Oxygenation Algorithm," MEDINFO '95 Proceedings of the Eighth World Congress of Medical Informatics, pp. 1132–36 ("Waisel")	1995	1011
Anderson, J.R. et al., "A Closed-Loop Controller for Mechanical Ventilation of Patients with ARDS," Technical Papers, Proceedings of the 39th Annual Rocky Mountain Bioengineering Symposium & 39th Int'l ISA Biomedical Sciences Instrumentation Symposium, Vol. 38, Presented at Copper Mountain, Colorado, April 12–14, 2002, pp. 289–94 ("Anderson")	April 12 -14, 2002	1013
Rossi, A. et al., "Intrinsic positive end-expiratory pressure (PEEPi)," Intensive Care Med (1995) 21:522–536 ("Rossi")	1995	1015

For each of the above-listed publications, Petitioner provides evidence to show "the authenticity of the documents" and "when and how each of these doc-

uments was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents." Declaration of Sylvia D. Hall-Ellis, Ph.D. (Ex. 1017), ¶ 12 (describing scope of the declaration), ¶¶ 51-68, 77-84, 94-110 (discussing above-listed references). Patent Owner has not challenged the prior art status of any of the cited references.[4] PO Resp., *passim*.

Petitioner also relies on the Declaration of Richard Imbruce (Ex. 1002) as evidence of the state of the art, the knowledge of one having ordinary skill in the art, and the anticipation and obviousness of the challenged claims based on the grounds presented in the Petition. Patent Owner supported its Preliminary Response with the Declaration of Fleur T. Tehrani (Ex. 2002) in rebuttal. Patent Owner supported its Patent Owner Response with the Second Declaration of Dr. Fleur Tehrani, dated March 31, 2021 (Ex. 2010).[5] Petitioner supported the Reply with a second

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[4] Patent Owner does make certain challenges to the admissibility of the references that we address in discussing Patent Owner's Motion to Exclude. *See infra* IV.

[5] The Tehrani Declaration and Second Tehrani Declaration both include two appendices that provide claim charts comparing the challenged claims to the disclosures in the prior art references relied on in the Petition. Ex. 2002, App. 1, App. 2; Ex. 2010, App. 1, App. 2. The Patent Owner Response attempts to incorporate by reference the arguments from these appendices. *E.g.*, PO Resp. 56, 65, 72. The AIA trial rules impose word limits for preliminary responses and prohibit incorporating arguments by reference from one document into another. 37 C.F.R. §§ 42.24(b)(1), 42.6(a)(3). We informed Patent Owner that we would not consider such incorporation by reference in our

Declaration of Richard Imbruce (Ex. 1029). Petitioner also submitted with its Reply the Declaration of Dr. Jeffrey R. Anderson, P.E. (Ex. 1028). Patent Owner filed two declarations with its Sur-Reply: the Third Declaration of Dr. Fleur Tehrani (Ex. 2022) and the Declaration of Dr. James H. Roum (Ex. 2026).

G. Prior Art and Asserted Grounds

Petitioner asserts that the challenged claims are unpatentable on the following grounds:

Claims Challenged	**35 U.S.C. §**	**References/Basis**
1, 2, 5, 6, 11, 29, 31–33, 41	102(b)	Carmichael
1, 2, 5, 6, 11, 29, 31–33, 41	103(a)	Carmichael (as evidenced by ARDSNET and Waisel) [6]

Institution Decision *and* our Rehearing Decision. *See* Inst. Dec. 9 n.4; Reh'g Dec. 3–5. Patent Owner has repeated this error. As explained in our Consolidated Trial Practice Guide (CTPG) (Nov. 2019), https://www.uspto.gov/TrialPracticeGuideConsolidated "parties that incorporate expert testimony by reference in their petitions, motions, or replies without providing explanation of such testimony risk having the testimony not considered by the Board." CTPG, 35–36 (citing *Cisco Systems, Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12 (PTAB Aug. 29, 2014) (informative)). We do not consider these appendices in reaching this Decision.

[6] Petitioner provides this obviousness ground as an alternative to the anticipation ground based on Carmichael. *See, e.g.*, Pet. 35–38. We list it as a separate ground because it is based on a different statutory provision than the anticipation ground.

1–6, 9–12, 29–33, 41	103(a)	Carmichael, Anderson, Tehrani '268, Rossi
1–6, 9–12, 29–33, 41	103(a)	Taube, Carmichael, ARDSNET, Clemmer, Rossi

II. Unpatentability Analysis

A. Legal Standards

Petitioner's first asserted ground of unpatentability is based on anticipation under 35 U.S.C. § 102(b). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). To establish anticipation, "all of the elements and limitations of the claim must be shown in a single prior reference, arranged as in the claim." *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001).

Petitioner's remaining asserted grounds of unpatentability are based on obviousness under 35 U.S.C. § 103.

> Section 103(a) forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of

underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when available, objective evidence, such as commercial success, long felt but unsolved needs, and failure of others.[7] *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[O]bviousness must be determined in light of *all the facts*, and . . . a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine" teachings from multiple references. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (emphasis added); *see also PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) ("The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact.").

B. Level of Ordinary Skill in the Art

The level of skill in the art is "a prism or lens" through which we view the prior art and the claimed invention. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Petitioner contends that a person having ordinary skill in the art of the '571 patent would be:

> (i) a medically trained physician or clinician specializing in treating respiratory failure issues with at least five years of practical clinical ventilator experience treating such

[7] The Patent Owner does not direct us to any objective evidence of non-obviousness in the current record.

> conditions; or (ii) a Master's degree in Electrical Engineering or a related field and about five years of practical experience with developing ventilators for clinical patient treatment; or (iii) a Bachelor's degree in Electrical Engineering or a related field and about 10 years of practical experience with developing ventilators for clinical patient treatment.

Pet. 20-21 (referencing Ex. 1002 ¶¶ 71-72). Petitioner proposes that "[a] higher level of education or specific skill might compensate less experience, and vice versa." *Id.* at 21.

Patent Owner does not present an opposing view of the level of skill of the hypothetical person having ordinary skill in the art of the '571 patent. *See* PO Resp. *passim*.

For the purposes of this Decision, we apply Petitioner's definition of the level of ordinary skill in the art. We determine that this definition is consistent with the prior art of record and the skill reflected in the Specification of the '571 patent, based on our review of the record.

C. Weight to Give Dr. Imbruce's Testimony

Patent Owner argues that we should disregard the testimony of Petitioner's Declarant. *See* PO Resp. 75–77; Sur-Reply 14–15. Patent Owner asserts that we should disregard Dr. Imbruce's testimony because he did "not identify[] that certain references had technically erroneous disclosures," he "was not forthcoming in his deposition," he "did not identify in his CV that he had been an expert witness in prior

matters." *Id.* Patent Owner located a case where his testimony had been excluded. *Id.* Patent Owner also argues that his testimony is unreliable because he testified that the claim term "for a next breath" was arbitrary and meaningless. *Id.*

We do not agree with Patent Owner that Dr. Imbruce's testimony should be disregarded. with respect to Patent Owner's contentions about "technically erroneous disclosures" and the construction of "for a next breath," those are really about Patent Owner's disagreements about those matters, not whether Dr. Imbruce was attempting to mislead the Board. Disagreement between the experts is not a basis for disregarding testimony. We have also reviewed the entirety of Dr. Imbruce's deposition, and, in particular, the various parts identified by Patent Owner. PO Resp. 76–77. And, contrary to Patent Owner's assertions, we found Dr. Imbruce gave detailed answers in response to Patent Owner's questions. We found Dr. Imbruce's testimony to be adequate. *See, e.g.*, Ex. 2016, 107:11–115:8 (discussion of Anderson references, explaining the similarities of the references, but declining to vouch for data he has not seen or collected); 115:9–116:6 (FDA permission, offering to confirm what reference said about FDA approval, but attorney moving on to other questions). Thus, we do not find Dr. Imbruce's behavior during cross examination as a reason to give no weight to the entirety of his testimony.

As for Patent Owner's complaint about the disclosure of his prior testimony, Patent Owner does not point us to any requirement that such testimony be disclosed. Moreover, Patent Owner was free to inquire of Dr. Imbruce on the topic, and did. *See* Ex. 2016, 13:14–17:19.

Patent Owner focuses on the exclusion of Dr. Imbruce's testimony in *Smith v. Terumo Cardiovascular Sys. Corp.* (Ex. 2017), but we do not find it informative about the weight we should give Dr. Imbruce's testimony in this case. The *Terumo* case dealt with failure analysis of a different device, and the court in *Terumo* excluded Dr. Imbruce's testimony because he was not an expert in failure analysis of such devices and applied a methodology that the party had abandoned, not whether he was knowledgeable about automated ventilators, the subject matter of this case. *See* Ex. 2017, 12–13. Indeed, the court explained

> Dr. Imbruce may have the knowledge to describe the general physiology of oxygenation. Dr. Imbruce may have the knowledge regarding the various medical devices he invented. But Dr. Imbruce does not have the knowledge to do a failure analysis and make the very specific determination that a Terumo System 1 heart-lung bypass machine failed due to software issues that had never been identified by the manufacturer or—from the available information—any other user of the System. . . .

Id. at 11.

Patent Owner also asserts that Dr. Imbruce's background does not match with the technology. Sur-Reply 15. As we explain below in response to Patent Owner's motion to exclude, there need not be a perfect match between the expert's qualifications and the patent at issue. *See SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010). It is not necessary for Dr. Imbruce to demonstrate that he spent the bulk of his career personally designing

mechanical ventilators. Indeed, to testify as an expert under Federal Rule of Evidence 702, a person need not be one of ordinary skill, but may be "qualified in the pertinent art." *See B/E Aerospace, Inc. v. MAG Aerospace Indus. LLC*, IPR2014-01513, Paper 104 at 13–14 (PTAB March 18, 2016) (Final Written Decision) (declining to exclude the testimony of expert witness that lacked hands-on experience with the claimed subject matter). We agree with Petitioner that Dr. Imbruce's lengthy experience, including: a) developing ventilator devices and work on a portable oxygen generator to provide emergency care to patients undergoing respiratory distress (Ex. 1003, Rapid Oxygen Company work; Ex. 2016, 10:23–12:22); (b) "developing clinical protocols for new modalities in artificial ventilation" in the relevant 2003–2009 time period of the patent at issue in this IPR; (c) "laboratory and clinical research funded by DOD developing oxygen delivery therapies to treat hemorrhagic shock in wounded soldiers" in the 2009–2016 time period (Ex. 1003); and (d) ongoing design and use of ventilators, provides him sufficient experience and knowledge of the claimed subject matter for his opinion to remain of record. Ex. 1003; Ex. 2016, 10:23–12:22.

Instead of disregarding Dr. Imbruce's testimony in its entirety, we evaluate each of his assertions on their own, in light of the explanation offered, his answers on the specific topics under cross examination, and the other evidence of record.

D. Claim Construction

In *inter partes* reviews, we interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action

under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

Petitioner offers express constructions for nine claim terms. Pet. 22– 27. Patent Owner offers express constructions for five claim terms. PO Resp. 11-13. Included in each party's initial claim construction briefing are proposed constructions for the means-plus-function claim terms "first means" and "second means" recited in claim 1. Pet. 22-23; Prelim. Resp. 12-13.

In our Institution Decision, we determined that only the claim terms "first means" and "second means" required construction. Inst. Dec. 25–27. Neither party disputes those constructions and we maintain and adopt them for the purposes of this Decision.

We determine that, for purposes of this decision, no other terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

E. Ground 1: Claims 1, 2, 5, 6, 11, 29, 31–33, and 41 as Anticipated by Carmichael

Petitioner contends that Carmichael anticipates independent claims 1 and 29, and claims 2, 5, 6, 11, 31-33, and 41, which depend from claim 1 or claim 29.

In the subsections below, we discuss the scope and content of Carmichael and the asserted anticipation of independent claims 1 and 29.

1. Carmichael

Carmichael is a publication reporting the results from a questionnaire sent to 3,164 physician members of the American Thoracic Society Critical Care Assembly asking the members' opinions regarding factors important in diagnosis and treatment of adult respiratory distress syndrome (ARDS). Ex. 1004, 9 (first col.). The data from the 31% of responding physicians was collected and reported. *Id.* The survey included questions about modes of mechanical ventilation used for treatment and how physicians apply PEEP at various levels of arterial oxygenation. *Id.* at 10 (first col.), 17-18 (questionnaire questions). The survey results showed that the initial treatment of patients with ARDS was most commonly accomplished using volume-cycled ventilation in the assist/control mode. *Id.* at 9 (first & second cols.), 11 (first col.) (disclosing, with reference to Figure 2, that assist/control was the favored ventilator mode). The survey results also showed that "[o]n average, oxygen toxicity was thought to begin at an F[i]O2 between 0.5 and 0.6," and that "modest levels of [PEEP] were used in incremental fashion as F[i]O2 requirements increased." *Id.* at 9 (second col.), 11 (second col.) (referencing Figure 4 showing level of FIO2 at which oxygen toxicity begins), 12 (second col.) (referencing Figure 7 showing the maximum PEEP used at various levels of FIO2 before increasing to the next higher level of FIO2). Carmichael also discloses that conventional teaching in the 1970s was that "a PaO2 > 60 mmHg was desirable and should be achieved through the use

of increased FiO2s and incremental application of PEEP." *Id.* at 13 (bottom of second col.)-14 (top of first col.). Carmichael discloses that in the early 1990s it was recognized that peak inspiratory pressures could induce lung injury and this understanding engendered interest in limiting peak inspiratory pressure. *Id.* at 14 (first col.). Carmichael reports that "[t]o many, the 'best PEEP' is the least PEEP at which hemoglobin-oxygen saturation is considered adequate on nontoxic concentrations of inspired oxygen." *Id.* at 14 (second col.).

2. Analysis of Claim 1

Petitioner asserts that Carmichael discloses an apparatus for automatically controlling a ventilator that includes the claimed "first means" for processing data indicative of at least a measured oxygen level of a patient, and for providing data indicative of FIO2 and PEEP for a next breath of the patient. Pet. 29-34. Specifically, Petitioner asserts that Carmichael's disclosed assist control mode uses the measured arterial oxygen level to provide data indicative of FIO2 and PEEP for a patient's next breath. *Id.* at 31 (referencing Ex. 1004, 11-12, Fig. 7). Petitioner asserts that Carmichael teaches a desirable PaO2 level achieved through the use of increased FIO2 and incremental applications of PEEP, teaching a level of PEEP that would not be exceeded before increasing to the next higher FIO2. *Id.* (referencing Ex. 1004, 12, 13-14).

Patent Owner argues that Carmichael discloses survey results "based on intermittent, manual, trial and error adjustment of FIO2 and PEEP." PO Resp. 29. Patent Owner argues that "in Carmichael, the FIO2 value is kept constant with PEEP being manually and

incrementally increased to some maximum level before the next change in FIO2" but in the '571 patent, "FIO2 is continuously determined based on the patient's measured oxygen level." *Id.* at 29–30 (emphasis omitted). In other words, Patent Owner argues that in Carmichael's trial-and-error system, "[n]o difference between a measured and desired oxygen level of a patient is defined and reduced as required by the claims of the patent. . . . " *Id.*

In our Institution Decision, we determined Petitioner had not shown a reasonable likelihood that Carmichael anticipates the challenged claims because it lacked adequate disclosure of the apparatus claimed. Inst. Dec. 29–30. In particular, we preliminarily found that "Carmichael lacks details as to the specific manner in which the assist control mode was being used to control PEEP and FIO2 levels" and whether Carmichael's disclosure "necessarily entails adjustments to FIO2 and PEEP." Inst. Dec. 30.

Petitioner argues that we should reconsider our initial finding because a qualified POSITA with hands-on clinical experience would have recognized Carmichael as necessarily disclosing determined adjustments of PEEP and FIO2 in providing control /data signals to "automatically control PEEP and FIO2 for a next breath of the patient." Pet. Reply 6. However, Petitioner states it "will focus on Ground 2 evidence of record," which supports a finding that Carmichael anticipates. *Id.*

We agree with Patent Owner that Carmichael lacks adequate disclosure to anticipate the apparatus of claim 1. Specifically, because Carmichael focuses on the result of physician surveys, and not on the description of a ventilation system per se, Carmichael

lacks details as to the specific manner in which the assist control mode was being used to control PEEP and FIO2 levels. Specifically, we cannot discern that Carmichael's discussion of an assist control mode for mechanical ventilation necessarily entails adjustments to FIO2 and PEEP "for a next breath of the patient" as recited in claim 1. As explained by Patent Owner, it is possible that the parameters of PEEP and FIO2 could have been set manually by the physician and/or could have been updated only periodically during treatment. *See, e.g.,* PO Resp. 25-26. Thus, Petitioner has not shown by a preponderance of evidence that Carmichael anticipates claim 1, or claims 2, 5, 6, and 11 that depend from claim 1.

3. Analysis of Claim 29

Independent method claim 29 recites the step of determining required FIO2 and PEEP for a patient and providing data signals indicative of the required FIO2 and PEEP "for a next breath of the patient." Ex. 1001, 15:19-30. Petitioner relies on the same findings as to the disclosure of Carmichael as discussed above in the analysis of claim 1. Pet. 41-43. For the same reasons discussed above, Petitioner has not shown by preponderance of the evidence that Carmichael anticipates claim 29, or claims 31-33 and 41 that depend from claim 29.

F. Ground 3: Claims 1-6, 9-12, 29-33, and 41 as Unpatentable over Carmichael, Anderson, Tehrani '268, and Rossi

Petitioner contends that the combination of Carmichael and Anderson renders obvious the subject matter of independent claims 1 and 29 and claims 2,

30, and 41, which depend from claim 1 or claim 29.[8] Petitioner contends that the combination of Carmichael, Anderson, and Tehrani '268 renders obvious the subject matter of dependent claims 3-6, 11, 12, and 31-33, and that the combination of Carmichael, Anderson, and Rossi renders obvious the subject matter of dependent claims 9 and 10. In the subsections below, we discuss the scope and content of the prior art and any differences between the claimed subject matter and the prior art.

1. Carmichael

A general discussion of Carmichael's disclosure is provided above in Section III.E.1.

2. Anderson

Anderson is a technical paper of The Instrumentation, Systems, and Automation Society (ISA), presented at the Proceedings of the 39th Annual Rocky Mountain Bioengineering Symposium and 39th Annual International ISA Biomedical Sciences Instrumentation Symposium. Ex. 1013. Anderson is a report describing a "closed-loop control system based on well-established protocols to systematically maintain appropriate levels of [PEEP] and [FiO2] in patients with [ARDS]." *Id.* at 289.

Anderson describes that the system consists of an in-dwelling arterial oxygenation (PaO2) sensor coupled to a computer that continuously controls FiO2 and PEEP settings on a Hamilton Amadeus ventilator. Ex.

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[8] Petitioner relies on only Carmichael and Anderson for claims 1, 2, 29–33, and 41. Tehrani '268 is added for claims 3–6, 11, and 12. Rossi is added for claims 9 and 10.

1013, 289; *see also id.* at 290, Fig. 1. Anderson acknowledges that "when high concentrations of inspired oxygen or high airway pressures become necessary in a very ill patient, the ventilator itself may further damage the patient's lungs." *Id.* at 290. Anderson states that "[t]he implemented protocols provide continuous closed-loop control of oxygenation and a balance between patient need and minimal therapy." *Id.* at 289. Specifically, "[t]he controller is based on a traditional proportional-integral-derivative (PID) approach . . . to control, or maintain, the patient's PaO2 level at a target value." *Id.* The controller also uses "non-linear and adaptive characteristics that allow the system to respond more aggressively to 'threatening' levels of PaO2." *Id.*

Anderson illustrates the basic elements of the closed-loop controller, in Figure 2 of Anderson, which is reproduced below:

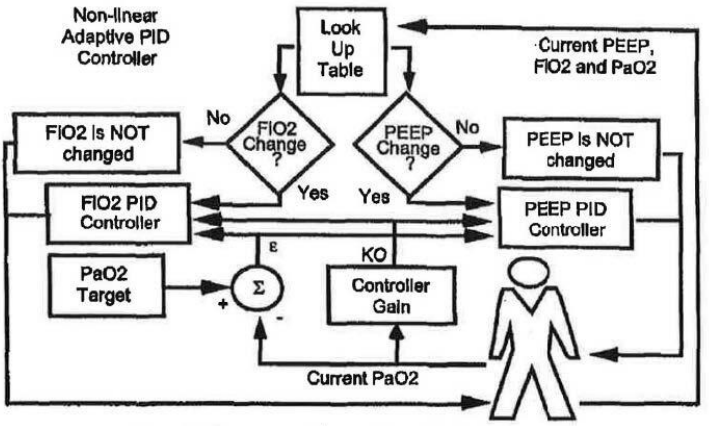

Figure 2. Components of the non-linear adaptive PID controller.

Ex. 1013, 291. Figure 2 of Anderson depicts "the look up tables or the decision mechanism, the FiO2 and PEEP PID controllers that calculate the amount of

therapy adjustment, and the adaptive overall gain term." *Id.*

Anderson describes that the look up tables "contain the logic used to dictate changes in therapy based on the patient's current level of PaO2 and the current PEEP and FiO2 settings." Ex. 1013, 291. Anderson shows five logic tables corresponding to different levels of patient blood oxygenation (*i.e.*, supersatisfactory, satisfactory, acceptable, marginal, and threatening) having physician-defined thresholds for each level. *Id.* at 291, Fig. 3. Anderson also discloses equations that "describe the discrete recursive form of the PID controller used to calculate the appropriate change in oxygenation therapy." *Id.* at 291 (equation #1 and equation #2). This PID controller uses gain to provide "more aggressive response to hypoxemia and a more conservative response to PaO2 above the desired goal." *Id.* at 292, Fig. 2 (showing graph of adaptive gain).

3. Tehrani '268

Tehrani '268 is a U.S. patent titled "Method and Apparatus for Controlling an Artificial Respirator." Ex. 1006, [54]. The patent relates to a method and apparatus for controlling a respirator based on the measured levels of carbon dioxide and oxygen of a patient on the respirator, as well as other physical conditions of the patient. *Id.* at 1:14-18. The patent describes a programmable microcomputer that uses the measured levels of carbon dioxide and oxygen of the patient to provide digital output data representing the amount and optimum frequency of ventilation required for the next breath. *Id.* at 2:2-7. Figure 1 of Tehrani '268 is reproduced below.

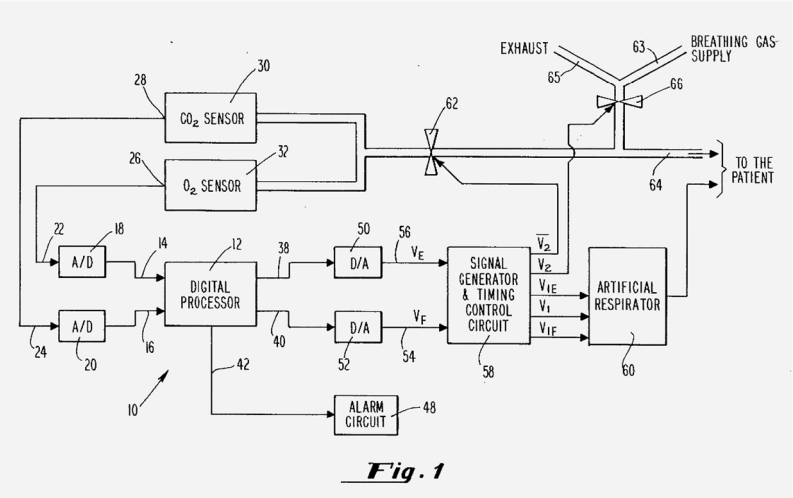

Fig. 1

Figure 1 is a block diagram of an artificial respirator and control apparatus. Ex. 1006, 2:35-37. The apparatus disclosed in Tehrani '268 includes A/D converters 18, 20 "coupled to the outputs 26 and 28 of an oxygen sensor 32 and a carbon dioxide sensor 30, respectively." *Id.* at 2:64-67. Tehrani '268 also discloses D/A converters 50 and 52 for control signals generated by the ventilator computer to be sent to analog components. *Id.* at 2:23-24. Tehrani '268 teaches that ventilators use measured values "supplied via the A/D converters" so that "they can also be monitored continuously." *Id.* at 3:8-11.

Tehrani '268 also describes that the apparatus calculates the pressures of oxygen and carbon dioxide in the patient's arterial blood, and compares these values to upper and lower alarm limits to generate an alarm if either pressure is outside of the specified range. *Id.* at 8:5-34.

4. Rossi

Rossi is a review article published in Intensive Care Medicine. Ex. 1015. Rossi describes that alveolar pressure can remain positive throughout expiration without PEEP set by the ventilator whenever the time available to breathe out is shorter than the time required to decompress the lungs to the elastic equilibrium volume of the total respiratory system. *Id.* at 522 (first col.). Rossi describes that this phenomenon has been termed "intrinsic PEEP [] owing to its similarity and contrast with PEEP set by the ventilator." *Id.* (first and second columns). Rossi describes that in assisted modes of mechanical ventilation, intrinsic PEEP (or PEEPi) should be measured routinely. *Id.* at 530 (first col.).

5. Analysis of Claim 1

Petitioner relies on Carmichael to disclose automated ventilators operating in assist control mode to provide prescribed ARDS treatment protocols. Pet. 46. Petitioner acknowledges that Carmichael does not disclose the ventilator architectures in detail. *Id.* Petitioner relies on Anderson to show a closed-loop control system using an oxygenation sensor and a computer to continuously control FIO2 and PEEP settings on a Hamilton Amadeus ventilator based on a traditional PID approach to control, or maintain, the patient's oxygen level at a target value. *Id.* at 46-47 (citing Ex. 1013, 289 (Abstract), 290, Fig. 1; Ex. 1002 ¶¶ 264-275). Petitioner asserts that a person of ordinary skill in the art would have been expected to implement Carmichael's disclosed PEEP/FIO2 treatment protocol on an automated ventilator, as disclosed by Anderson, to "systematically maintain appropriate levels of [PEEP]

and [FIO2]." *Id.* at 47 (quoting Ex. 1013, 289). Petitioner asserts that operation of Anderson's ventilator according to Carmichael's treatment protocol of "determining PEEP, after determining [FIO2], to keep a calculated ratio of PEEP/[FIO2] within a prescribed range would have been predictable and routine ventilator operation." *Id.* at 47-48 (referencing Ex. 1002 ¶¶ 273-275).

Petitioner has shown by a preponderance of the evidence that Carmichael discloses it was known in the art at the time of the invention to use volume-cycled ventilation in the assist/control mode to implement treatment protocols for treatment of ARDS patients through automatic control of a ventilator. Pet. 29-30; Ex. 1004, 9 (first & second cols.), 11 (first col.); Ex. 1002 ¶¶ 119-123. Petitioner has shown that Carmichael discloses a treatment protocol of increased FIO2 and incremental application of PEEP at the FIO2 level to achieve a desired oxygen saturation level. Pet. 30-31; Ex. 1004, 11 (second col.) (referencing Figure 4 showing level of FIO2 at which oxygen toxicity begins), 12 (second col.) (referencing Figure 7 showing the maximum PEEP used at various levels of FIO2 before increasing to the next higher level of FIO2), 13 (bottom of second col.), 14 (top of first col.) (conventional teaching was that "a PaO2 > 60 mmHg was desirable and should be achieved through the use of increased FiO2s and incremental application of PEEP"); Ex. 1002 ¶¶ 124-127. Petitioner has shown that Carmichael discloses "[t]oo [sic] many, the 'best PEEP' is the least PEEP at which hemoglobin-oxygen saturation is considered adequate on nontoxic concentrations of inspired oxygen." *Id.* at 14 (second col.). Thus, Peti-

tioner has shown that Carmichael discloses a relationship between FIO2 and PEEP used to achieve a desired oxygen saturation. Petitioner also has shown that Carmichael's treatment protocol determines FIO2 to reduce the difference between the measured oxygen level of the patient and a desired value. Pet. 32; Ex. 1004, 13-14 (describing selection of FIO2 to achieve a desired oxygen saturation (PaO2 > 60 mmHG)); Ex. 1002 ¶ 136.

Petitioner has also shown that Anderson discloses a closed-loop automated ventilator and control system for continuous control of PEEP and FIO2 based on oxygen saturation. Pet. 46-47. Petitioner has shown that the treatment protocol disclosed in Carmichael, as implemented, with a reasonable expectation of success, on the closed-loop continuous control system of Anderson, would include the claimed first means (or equivalents thereof) for determining PEEP and FIO2 in the manner claimed and the claimed second means (or equivalents thereof) for providing signals to control the ventilator by automatically controlling PEEP and FIO2 for a next breath of the patient. Pet. 46-48; Pet. Reply 18–19 (citing Ex. 1002 ¶¶ 147, 274, 275, 290).

As to Carmichael, Patent Owner argues that the main outputs of the ventilator are set manually by an operator by trial and error and are not automatically controlled. PO Resp. 23-27 (citing Ex. 2007, 2012). Exhibit 2007, cited by Patent Owner, is a 1992 paper presented during a conference on the "Essentials of Mechanical Ventilators." Ex. 2007, 1026. This paper describes that "Assist/control ventilation (A/C) is a mode of ventilator operation in which mandatory breaths are delivered at a set [frequency], pressure or

volume, and inspiratory flow. Between machine-initiated breaths, the patient can trigger the ventilator and receive a mandatory breath at the volume or pressure set on the ventilator." *Id.* at 1032. Exhibit 2012, which is cited by Patent Owner, is an article from "RT Magazine," dated February 7, 2007. Ex. 2012, 1. Exhibit 2012, to the extent it has any weight as it is from long after the filing of the challenged patent, provides a similar understanding. Ex. 2012, 2 ("ACMV still delivers a set tidal volume at a set respiratory rate, but also responds to a patient's inspiration."). We disagree with Patent Owner's premise that an apparatus "for automatically controlling a ventilator" must provide automatic control of some of the outputs "for a next breath of the patient." PO Resp. 26, 58–59. The preamble of the challenged independent claims, which is where Carmichael is cited by itself for disclosing automatic control of a ventilator, does not recite "for a next breath of the patient." Ex. 1001, 12:48-49, 15:15-16. Petitioner relies on the combination of the references where the claim does recite "for a next breath of a patient. *See* Pet. 46–48. Indeed, the Specification of the '571 patent describes a clinician manually setting the initial values and allows for manual control of PEEP in the preferred embodiment of the invention. *Id.* at 7:67–8:2, 8:10–14, 10:16–65, 11:48–49, 12:23–28. Thus, Patent Owner's argument that "[a]n automatic ventilator cannot have manually set outputs that are adjusted intermittently by an operator" is inconsistent with the description in the challenged patent. *See* PO Resp. 58. Our finding that Carmichael discloses automatic control of a ventilator is based on our understanding that Carmichael discloses a ventilator that allows an operator to select a desired PEEP and FIO2, and the ventilator controls

the output to deliver machine initiated breaths at these desired values. Ex. 1002 ¶¶ 122, 123. This understanding is supported by Petitioner's evidence and is consistent with the description of "assist/control ventilation" provided in Patent Owner's Exhibit 2007.

Further, this ground is based on the modification of Carmichael's assist control ventilator with Anderson's automated ventilator architecture to provide automated control for a next breath of the patient. Pet. 46-48. The record contains extensive evidence that highly sophisticated microprocessor-controlled ventilator systems capable of very high gas outputs, complex monitoring were known in the art at the time of the invention. *See* Ex. 1011 (Waisel), 1132 (§ 2), 1134 (§ 2.3); Ex. 1013 (Anderson); Ex. 1006 (Tehrani '268). Thus, Patent Owner's separate attack on Carmichael is simply not persuasive when the Petition relies on the combination of references.

Patent Owner also argues that Carmichael fails to disclose that PEEP is determined to keep a ratio of PEEP/FIO2 within a prescribed range. PO Resp. 27–30. As discussed above, Petitioner has shown that Carmichael disclosed it was known in the art to select PEEP based on the level of FIO2 and to avoid exceeding a maximum PEEP for a certain FIO2 by moving to next higher level of FIO2 when the PEEP reaches the maximum level. Ex. 1004, 12, Fig. 7. Figure 7 of Carmichael shows that the maximum level of acceptable PEEP increased as the FIO2 level increased. *Id.* Petitioner describes, and we find persuasive, how this disclosed protocol selects PEEP to maintain a ratio of PEEP/FIO2 within a certain range. Pet. 32-33.

Patent Owner argues that "[b]y trial and error adjustment, FIO2 is not determined to reduce the difference between the measured oxygen level of a patient and a desired value as required in the Patent." PO Resp. 27 ("There is no mechanism in place to reduce such difference systematically"). As discussed above, Petitioner has shown that Carmichael discloses adjusting FIO2 to reach a desired oxygen level. *See* Ex. 1002 ¶¶ 129–135. Patent Owner's arguments about trial-and-error are beside the point. Importantly, even if clinicians in Carmichael reached their preferred treatment by trial-and-error, Carmichael reports this preferred treatment, which a person of ordinary skill would have been motivated to implement in the automated system of Anderson with a reasonable expectation of success. *See* Ex. 1002 ¶¶ 267–275. We find sufficient evidence and reasoning that one having ordinary skill in the art, implementing such a protocol to adjust FIO2 to reach a desired oxygen level, as taught in Carmichael, in the automated system of Anderson, would have been led to adjust FIO2 to minimize the difference between the measured and desired oxygen levels.

As to Anderson, Patent Owner also argues that Anderson's disclosure of a look up table to control PEEP and FIO2 suggests discrete pairs for intermittent adjustments of the two variables, while Anderson's "Proportional-Integral-Derivative (PID) controllers are designed to control the output continuously and based on error signals." PO Resp. 35, 62. Patent Owner argues that these two techniques are contradictory means of adjusting PEEP and FIO2. *Id.* at 36. We disagree that Anderson is internally inconsistent. Anderson discloses that the look up tables shown in

Figure 3 contain the logic used to dictate if changes in therapy are needed "based on the patient's current level of PaO2 and the current PEEP and FiO2 settings." Ex. 1013, 291. Thus, these logic tables are used to determine whether a change in PEEP and/or a change in FIO2 is necessary. *Id.* at Fig. 3 (showing indicators of "B" when both PEEP and FIO2 are to be changed, an "F" if only FIO2 is to be changed, a "P" if only PEEP is to be changed, and "N" if neither is to be changed); Ex. 1028 ¶¶ 16–18; Ex. 1029 ¶¶ 6, 7, 11. Anderson discloses that the look up tables contain "logic used to dictate changes in therapy based on the patient's current level of PaO2 and the current PEEP and FiO2 settings." Ex. 1013, 291. Different "tables correspond to different levels of patient blood oxygenation." *Id.* PID equations then control FIO2 and PEEP settings. Ex. 1013, 291–292, eqs.1–2, Fig. 4. Anderson does not disclose using these look up tables to determine the amount of the change to either or both of these parameters. Rather, Anderson uses equations to calculate the appropriate changes. *Id.* at 291 (eq. #1, eq. #2), Fig. 2 (describing using the FIO2 and PEEP PID controllers to determine the amount of change needed); Pet. Reply 16 (showing annotated version of Figure 7 of Anderson showing FiO2 being adjusted while PEEP is maintained and then both being adjusted later).

We further note the similarity of Anderson's use of Lookup Tables to the Loop Indicators (LIs) of the '571 Patent, which operate in conjunction with PID control. Pet. Reply 16. As Petitioner explains, a selected look up table (LUT) of Anderson defines logic to apply PID control of PEEP and FIO2. *Id.* A selected

loop indicator of the '571 Patent does the same. Ex. 1001, 8:23–25; Figs. 3a–3h: steps 212, 224–226, 252.

Patent Owner further argues that the equations disclosed in Anderson for PID control "are erroneous." PO Resp. 37. Patent Owner points to Anderson's disclosure that the equations are for the "discrete recursive form of the PID controller." *Id.* (citing Ex. 1013, 291). Patent Owner then argues that "[t]he parameters of a discretized PID are functions of the sampling interval and are not constant," citing "equation 8-52 on page 312 of Exhibit 2013." *Id.* We have reviewed Exhibit 2013, and fail to see on its face, and Patent Owner does not provide adequate explanation, exactly how it supports Patent Owner's assertions.[9] Patent Owner further argues that "discretized PID is not applicable to the subject of Anderson." *Id.* Again, Patent Owner does not cite to any evidence in its Patent Owner Response to support these arguments, nor does Patent Owner provide in its Patent Owner Response any explanation for the basis of these assertions.[10] In contrast, Dr. Anderson confirms in his testimony that the equations are accurate. Ex. 1028 ¶ 15. We find this testimony consistent with the disclosure of Anderson and give it significant weight.

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[9] Dr. Tehrani makes identical allegations in her declaration. Ex. 2010 ¶ 83. However, no additional explanation is provided in that paragraph. *Id.*

[10] Although not cited in the Patent Owner Response, Patent Owner provides similar assertions in her declaration without any further explanation or reasoning to explain the basis for these assertions. Ex. 2010 ¶ 83. We decline to give weight to this unsupported testimony.

Patent Owner seeks to have us infer that Anderson's system did not use any PID control, despite Anderson's explicit disclosure of PID controllers, because the clinical results reported in Anderson are identical to results in the 1994 Anderson paper (Ex. 2008) published eight years earlier. PO Resp. 37–40, 60–62. Patent Owner asserts that this earlier article describes that the system "is 'protocol' based as stated in the paper (meaning it used a look up table) and it does not use any PID controller." *Id.* at 40. Patent Owner argues that because Anderson's results are the same as the 1994 paper (Ex. 2008), it appears the authors used only a look up table for both articles. *Id.*; Ex. 2010 ¶¶ 84–87. Patent Owner bases this contention on an interpretation of the sentence "A system was designed based on these protocols which provides continuous closed-loop control of oxygenation." Ex. 2008, A188; Ex. 2010 ¶¶ 83–87, 141–150.

We decline to ignore Anderson's explicit teaching of use of PID controllers to determine the amount of change needed for continuous adjustment of PEEP and FIO2. We also decline to infer that the mention in the 1994 Anderson paper to the use of "protocols" to design its closed-loop system necessarily means that the earlier system in the 1994 Anderson paper was based solely on look up tables. Ex. 2008 ("A system was designed based on these protocols which provides continuous closed-loop control of oxygenation"). The 1994 Anderson paper is silent as to the particular logic used in its software to provide the control of PEEP and FIO2. *Id.* The natural reading of Anderson's discussion of "protocols" is that a treatment protocol was developed by clinicians and the system was designed "based on" that "protocol," and nothing more. Ex. 2008, A188.

This conclusion is further supported by the testimony of Dr. Anderson. *See* Ex. 1028 ¶¶ 3–5. Dr. Anderson acknowledges that the data included in the two papers is the same, and explains that the "protocols" discussed are the treatment protocols developed by some of the co-authors, not the architecture of the system. Ex. 1028 ¶¶ 7, 8. This testimony and our reading is consistent with the two papers when they are read together. The 1994 Andersen paper (Exhibit 2008) is a brief synopsis of the work in progress, less than a half a page long. It provides minimal details regarding the architecture of the system. *See generally* Ex. 2008. The Anderson reference (Exhibit 1013) is a lengthy detailed description of the work. *See generally* Ex. 1013. We note that Exhibit 1013 contains a similar description of the design criteria to Exhibit 2008: "We have designed a system based on well-established protocols for management of mechanical ventilation that provides continuous loop control of oxygenation and a balance between patient need and minimal therapy." Ex. 1013, 290. Thus, Exhibit 1013 is consistent with Exhibit 2008.

Patent Owner's reading of these two papers—where Exhibit 2008's use of the word "protocol" must mean that the system used look up tables and, therefore, Exhibit 1013 is a falsified article—is unreasonable, takes the word "protocol" as it is used in Exhibit 2008 entirely out of context, ignores the more natural reading of the two papers together, and goes against Dr. Anderson's unimpeached and well-explained testimony. Patent Owner's accusations are serious ones, but are based on nothing more than conjecture and suspicions. We find Patent Owner's contentions unsupported and against the great weight

of the evidence. Thus, we disagree with Patent Owner that Anderson should be disregarded.

Patent Owner contends that experiments, such as Anderson's, require FDA approval, but Anderson does not "provide the essential and required information about an FDA permission to conduct its claimed closed-loop clinical experiments." PO Resp. 40–41. Patent Owner's argument is not persuasive. Patent Owner points to no evidence that any article about a study must discuss FDA permission specifically. *See id.* And there is no requirement that a party submit an FDA number to the Board to show something is prior art. *See* 35 U.S.C. § 102. Anderson explicitly discloses clinical compliance of trials conducted in Salt Lake City, Utah, where "Informed consent was obtained from 2 ARDS patients in the Shock/Trauma ICU at LDS Hospital for a clinical trial." Ex. 1013, 292. Dr. Anderson's testimony confirms that the proper approvals were obtained for the trial. Ex. 1028 ¶¶ 5–14, 19–22. Patent Owner cites FDA documents apparently from 2006—long after the trial discussed in Anderson took place. Exs. 2014, 2015. However, even if we consider these documents from long after the trial, at most, all these FDA documents suggest is that FDA permission must be obtained for such clinical trials. *Id.* Patent Owner fails to point out any requirement that any paper describing such clinical trials must explicitly discuss FDA approval of the study they are describing. *See* PO Resp. 40–41; Sur-Reply 30–31. Thus, Patent Owner's conclusion that no clinical trial actually took place because the article does not contain evidence of FDA permission is com-

pletely speculative, wholly without evidentiary support, and against the entire weight of the evidence in the record.

Finally, Patent Owner argues that Anderson's use of a PID controller would result in constant changing to PEEP that would be hazardous to a patient, which is why no commercial ventilator has used a PID controller to control PEEP. PO Resp. 41. Patent Owner does not cite to any evidence in its Patent Owner Response to support this assertion.[11]

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[11] We note that Patent Owner's argument that continuous changing of PEEP is "against the method of the patent" is directly in tension with Patent Owner's proposed construction of "for a next breath of the patient." PO Resp. 11–12, 42. For claim construction, Patent Owner argues that "[t]he term "for a next breath of the patient" simply means "for a patient's breath immediately following in time" or simply "the next breathing cycle of the patient" as evident from the claims and the entire patent specification." *Id.* at 12. However, with respect to Anderson and Taube, Patent Owner argues that adjusting FIO2 is required, but adjusting PEEP breath-by-breath is forbidden. Indeed, Patent Owner asserts that the Specification discloses only adjusting PEEP after a 240 second delay. *See* PO Resp. 41 ("In the Patent, PEEP is determined (*i.e.*, decided upon) every fraction of a second (*e.g.*, every 0.75 seconds as shown in Figure 3h) and for a next breath of the patient, but it is not 'changed' until a fixed period (*e.g.*, 240 seconds) has passed since the last 'change' in PEEP."). The challenged claims make no distinction between FIO2 and PEEP, but instead recite automatically controlling both of them "for a next breath of a patient." *See, e.g.*, Ex. 1001, 13:1–3 ("wherein the control signals provided to the ventilator *automatically control PEEP, and FIO2*, *for a next breath of the patient*" (emphasis added)). Without meaningful explanation, Patent Owner would have "for a next breath of the patient" mean different things for different parts of the *same limitation*. We do not need to resolve this tension between the proposed claim construction and these admissions regarding the disclosure of the challenged patent, because we determine that regardless of

Patent Owner does cite to its declarant's testimony on this point, but the declaration cites no other evidence to support the factual contentions underlying this opinion. Ex. 2010 ¶ 92. Thus, we give this testimony little weight. Anderson discloses that its clinical results showed that the system disclosed in Anderson was safe for control of PEEP and FIO2 in the patients on which it was tested. Ex. 1013, 293. Dr. Anderson provides similar testimony as to the safety and efficacy of the system. Ex. 1028 ¶¶ 7–14. Thus, we find that the preponderance of the evidence in this record does not support Patent Owner's contentions.

Moreover, even if Patent Owner were correct regarding this contention about adjusting PEEP, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Patent Owner fails to explain how PID control would be outside the scope of the language of the claims. Instead, Patent Owner agreed that PID control was within the meaning of "determining" and "calculating." *See* PO Resp. 13; Ex. 1027, 116:25–117:3.

As to the combination, Patent Owner argues that Anderson's alleged system would be rendered inoperable if combined with Carmichael's manual setting of parameters. PO Resp. 73–75. This argument misstates Petitioner's proposed combination. Petitioner does not propose to modify Anderson's automated ventilator

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whether we adopt Patent Owner's or Petitioner's claim construction, Grounds 3 and 4 meet this limitation.

control system to use manual controls. Rather, Petitioner proposes that it would have been obvious to employ Anderson's automated system to implement Carmichael's treatment protocol for adjustment of PEEP and FIO2 in ARDS patients. Pet. 47–48. "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference," *In re Keller*, 642 F.2d at 425; *see also In re Mouttet*, 686 F.3d at 1332 (citing *In re Keller*, 642 F.2d at 425), but rather whether "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Anderson itself describes that existing treatment protocols were used to design the system. Ex. 1013, 290. This goal is reflected in other references in this art in the record as well. *See, e.g.*, Ex. 1011, 1133 (noting the goal of "mimic[ing] how expert clinicians care for patients").

Patent Owner also asserts that the Petitioner never specifically addresses how Anderson determines FIO2 and PEEP "for a next breath of the patient." PO Resp. 62. Petitioner describes, with reference to Figure 1 of Anderson, that Anderson's "computer constantly reads important information from both the PaO2 monitor and Ventilator via RS232 serial ports" and uses this information "to calculate new values of PEEP and FiO2 that are subsequently transmitted to the ventilator for proper adjustments in patient therapy." Pet. 47 (citing Ex. 1002 ¶¶ 271–272; Ex. 1013, 290). Petitioner's declarant, Dr. Imbruce, explains

in the cited paragraphs that the closed-loop adaptive controller of Anderson's Figure 2 "continuously controls FiO2 and PEEP." Ex. 1002 ¶ 272 (citing Ex. 1013, 291). Carmichael's protocol targets a desired PaO2 level "through the use of increased FiO2s [sic] and incremental application of PEEP" while keeping PEEP to a value within a range of zero to 25 cm H2O for a given FIO2 value. Ex. 1004, 13–14; Ex. 1002 ¶ 147. We understand Petitioner, in its contentions that the computer "constantly reads" information from the patient and "continuously controls FiO2 and PEEP," to address the requirement that the system determines FIO2 and PEEP "for a next breath of the patient" in view of Carmichael's teachings.

For these reasons, Petitioner has demonstrated by a preponderance of the evidence that claim 1 would have been obvious based on the combined teachings of Carmichael and Anderson.

6. Analysis of Claim 29

Petitioner relies on the same findings and combination of Carmichael and Anderson to challenge method claim 29 as presented for its challenge to claim 1. Pet. 57-58. Patent Owner does not present separate arguments for claim 29. *See* PO Resp. 10, 11, 27, 29, 35–43, 56–65, 72-75 (presenting the same arguments for claims 1 and 29). We have reviewed Petitioner's evidence and arguments for claim 29, and find them sufficient. *See* Pet. 57– 58. Thus, for the same reasons discussed above in our analysis of claim 1, Petitioner has shown by a preponderance of the evidence that claim 29 would have been obvious based on the combined teachings of Carmichael and Anderson.

7. Analysis of Claims 2-6, 9-12, 30-33, and 41

Claims 2-6, 9-12, 30-33, and 41 all depend directly or indirectly from claim 1 or claim 29. We have reviewed Petitioner's cited evidence and explanation regarding why the combination of Carmichael and Anderson, either by itself, or further combined with Tehrani '268 and Rossi, renders obvious the subject matter of these dependent claims and find the evidence and reasoning sufficient to show by a preponderance of the evidence that these claims are unpatentable. Although Patent Owner discusses Tehrani '268 in its Patent Owner Response, Patent Owner does not address or contest Petitioner's reliance on Tehrani '268 for its disclosure of an A/D converter or a D/A converter (claim 5, 10, 31). PO Resp. 54-55 (arguing only that Tehrani '268 does not disclose certain subject matter of claims 1 and 29 and does not disclose the features of unchallenged claim 14). Patent Owner argues that Petitioner's reliance on Tehrani '268 for teaching an alarm unit (claims 3, 4, 11, 12) is misplaced. PO Resp. 55. We disagree. Petitioner has shown persuasively that the combined teachings of Carmichael, Anderson, and Tehrani '268 would have rendered the subject matter of these claims obvious. Pet. 48-50; Ex. 1002 ¶¶ 277-295 (demonstrating that it was well-known in the art of automated control for a ventilator computer to detect an artifact and generate an alarm output).

Further, although Patent Owner discusses Rossi in its Patent Owner Response, Patent Owner does not contest Petitioner's reliance on Rossi for its disclosure of measurement of PEEPi (claims 9, 10, 30). PO Resp. 53-54 (arguing that Rossi individually does not

describe any system to control a ventilator or to control PEEP, and not presenting arguments against Rossi in combination with the teachings of Carmichael and Anderson).

Patent Owner raises no other arguments regarding these claims other than those considered above with respect to claim 1. We determine that Petitioner has shown by a preponderance of the evidence that the combined teachings of Carmichael, Anderson, Tehrani '268, and Rossi render obvious claims 2-6, 9-12, 30-33, and 41.

G. Ground 4: Claims 1-6, 9-12, 29-33, and 41 as Unpatentable over *Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi*

Petitioner contends that the combination of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi renders obvious independent claims 1 and 29, and claims 2-6, 9-12, 30-33, and 41, which depend from claim 1 or claim 29. In the subsections below, we discuss the scope and content of the prior art and any differences between the claimed subject matter and the prior art.

1. Taube

Taube is a U.S. patent titled, "Adaptive Controller for Automatic Ventilators." Ex. 1005. Taube describes automatic controls for positive pressure ventilation systems. *Id.* at 1:6-8. Specifically, Taube's system is intended to make more automatic the control of inspiratory ventilation time (Tinsp), PEEP, and FIO2. *Id.* at 1:25-30. Taube discloses using a pulse oximeter to determine hemoglobin saturation and of

the patient's blood to calculate the partial pressure of arterial oxygen (PaO2), which is used to regulate Tinsp, PEEP, and FIO2. *Id.* at 1:31-37. Taube describes, "[t]he control mechanism is derived from the known relationship between the preset level of Tinsp, PEEP, minimum required FiO2 delivered to the patient, and predetermined lung function dynamics in order to maintain a desirable PaO2." *Id.* at 1:37-41.

Taube describes prior art devices for controlling the oxygen content of blood by controlling breathing parameters, and using an optical oximeter and a temporary oxygen deficient mixture to prevent super saturation. *Id.* at 1:62-2:66. Taube describes using sensed hemoglobin saturation to concurrently and adaptively control FIO2, Tinsp, and PEEP from a ventilator to address "the patient's changing need for increasing and decreasing of blood oxygenation." *Id.* at 2:67-3:7. Taube's system automatically provides "the highest oxygen saturation in the blood" while maintaining the highest possible Tinsp, the lowest possible PEEP, and the lowest possible FIO2 delivered to the patient. *Id.* at 3:15-29.

Figure 1 of Taube is shown below.

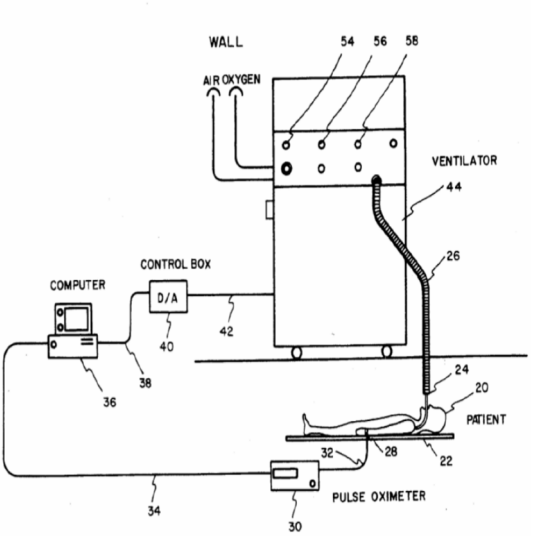

FIG. 1

Figure 1 of Taube is a diagrammatic view of the automatic ventilator control system. Ex. 1005, 3:64-65. Figure 1 shows optical sensor 28 placed on the finger of patient 20. *Id.* at 4:17. Pulse oximeter 30 is connected to sensor 28 and computer 36. *Id.* at 4:18-24. The outputs from computer 36 pass through D/A converter 40 to ventilator 44. *Id.* at 4:24-26.

Taube discloses the control program with reference to Figure 3, which is reproduced below.

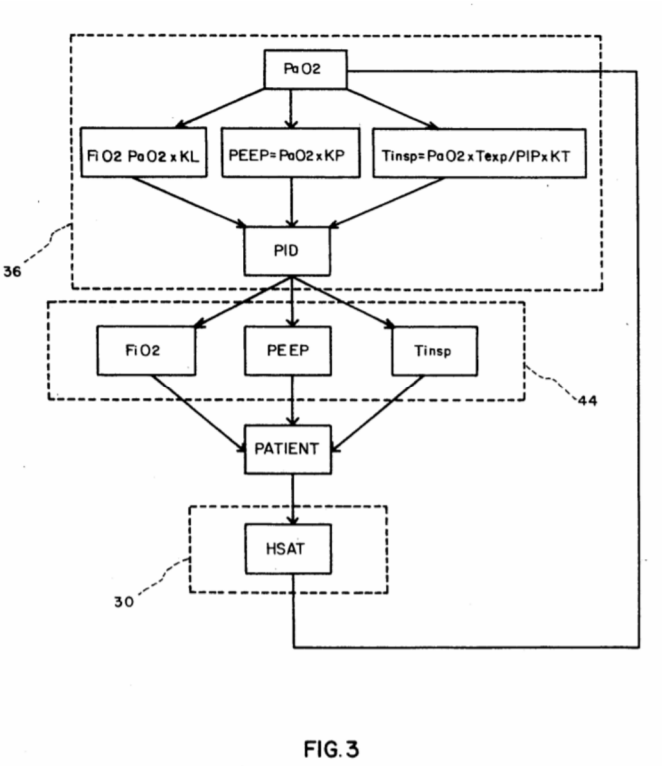

FIG. 3

Figure 3 is a flow diagram showing the operation of Taube's system. Ex. 1005, 3:67-68. Taube describes that computer 36 receives a hemoglobin saturation signal from pulse oximeter 30 and calculates a partial pressure of arterial oxygen (PaO2) value for patient 20. *Id.* at 5:16-18. According to Taube, "The computer then determines modification values of Tinsp, PEEP, and FiO2 from the calculated PaO2." *Id.* at 5:19-21. After the modification values are determined, the "computer then determines the proportional, differential, and integral gain coefficients to develop control signals to the ventilator" and "sends control signals to the ventilator for the modification of Tinsp, PEEP, and FiO2 values." *Id.* at 5:22-27. Taube then describes

that "[t]he patient then breath[e]s in through a breathing tube the positive air pressure at the modified Tinsp, PEEP, and FiO2 values." *Id.* at 5:28-30. Taube explains that "[t]he values of Tinsp, PEEP, and FiO2 are chosen by the computer to maintain a desired level of the patient's blood oxygen level." *Id.* at 5:30-33.

2. Carmichael

A general discussion of Carmichael's disclosure is provided above in Section II.E.1.

3. ARDSNET

ARDSNET is an article published in The New England Journal of Medicine reporting on the results of a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in patients with acute lung injury and ARDS. Ex. 1007, 1301 (Background). The article provides a table summarizing the ventilator procedures used during the trial. *Id.* at 1303 (Table 1). The table shows that the trial treated two groups of patients, a first group receiving traditional tidal volumes and a second group receiving lower tidal volumes. *Id.* Both groups were treated with a "volume assist-control" ventilator and using an oxygenation goal of PaO2 of 55-80 mm Hg or SpO2 of 88-95%. *Id.* The Table lists a range of "allowable combinations of [FIO2] and PEEP" that includes FIO2 of 0.3 to 1.0 and PEEP of 5 to 24 cm of water. *Id.* ARDSNET describes that various data were recorded "in four hours before the ventilator settings were changed on day 0" and that data "were recorded between 6 and 10 a.m. on days 1, 2, 3, 4, 7, 14, 21, and 28." *Id.* at 1303.

4. Clemmer

Clemmer is a U.S. patent titled, "Method and System for Patient Monitoring and Respiratory Assistance Control Through Mechanical Ventilation by the Use of Deterministic Protocols." Ex. 1008, [54]. Clemmer describes its objective as generating executable instructions for patient care which takes into account a large number of parameters of patient conditions and ventilation. *Id.* at [57]. "Patient data are processed according to a set of protocols which contain rules for patient care decisions arranged in a logical sequence to generate detailed, executable instructions for patient care." *Id.* The data can be acquired and the patient care instructions can be carried out automatically, and instructions are updated when new data is acquired. *Id.* Specifically, Clemmer describes monitoring and controlling a patient's oxygenation while being treated through mechanical ventilation by controlling the patient's oxygen partial pressure by adjusting PEEP and FiO2. *Id.* at 5:65-6:1. Clemmer describes various protocols for generating patient care instructions. *Id.* at Figs. 2-18B.

5. Rossi

A general discussion of Rossi's disclosure is provided above in Section II.F.4.

6. Analysis of Claim 1

Petitioner relies on Taube to disclose automated control of a ventilator to adjust PEEP and FIO2. Pet. 61. Petitioner maps Taube's ventilation system to the first means and second means of claim 1. *Id.* at 61-63 (citing Ex. 1005, 1:25-30, 1:37-41, 4:30-50, 5:8-6:15, Fig. 1; Ex. 1002 ¶¶ 409-412). Petitioner acknowledges

that Taube does not explicitly discuss a desired value for a hemoglobin saturation setpoint. *Id.* at 64.

Petitioner asserts that Carmichael discloses a desired setpoint of "oxygen saturations of 86% to 90%" and discloses monitoring a patient's measured oxygen saturation level and increasing FIO2 and incremental application of PEEP to bring the patient's oxygen saturation closer to the setpoint. Pet. 64 (citing Ex. 1004, 13-14; Ex. 1002 ¶¶ 413-418). Petitioner asserts that a person of ordinary skill in the art would have been motivated to modify Taube's ventilator system control to keep the PEEP/FIO2 ratio within a prescribed range, as disclosed by Carmichael, "to ensure that mechanical ventilation would improve important clinical outcomes in patients by keeping the patient's hemoglobin saturation closer to the desired 'oxygen saturations of 86% to 90%' [] while avoiding an application of PEEP that could be higher than a permissible maximum value." *Id.* at 64-65 (citing Ex. 1004, 12-14; Ex. 1002 ¶¶ 419-430).

Petitioner relies on Clemmer as "evidence of the skill level in the art for programming an automated ventilator with any of a variety of treatment protocols" and to show that modifying Taube's system to use Carmichael's treatment protocols would have involved "known programming techniques and constituted a predictable, expected result." Pet. 66. On review of the entire record, Petitioner has shown by a preponderance of the evidence that claim 1 would have been obvious over the combination of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi.

Pointing to Figure 3 of Taube, Patent Owner argues that Taube differs from claim 1 because in Taube, if PaO2 increases (*i.e.*, an improvement in oxygenation),

then the levels of FIO2, PEEP, and Tinsp are increased. PO Resp. 49; *see also id.* at 50-51; Sur-Reply 28–29. Patent Owner argues that Taube's control algorithm is against clinical practice, in which levels of PEEP and FIO2 are increased if the oxygen level decreases. *Id.* Patent Owner's characterization of Taube's Figure 3 appears overly simplistic. When Figure 3 is considered in combination with the accompanying description, Taube teaches that the computer chooses the values of the parameters (FIO2, PEEP, Tinsp) "to maintain a desired level of the patient's blood oxygen level." Ex. 1005, 5:30–33. Taube also recognizes, discussing the prior art, the problem of oversaturation. Ex. 1005, 2:14–20. We agree with Dr. Imbruce, and give substantial weight to his testimony, that Patent Owner's reading of Taube is unreasonable and contrary to Taube's own disclosure. *See* Ex. 1029 ¶¶ 13–19. Thus, we do not understand Taube to disclose in Figure 3 a system that continues to increase PEEP and FIO2 levels as the patient's oxygen levels increase.[12]

Patent Owner acknowledges that Taube's Figure 3 shows adjustment of PEEP, FIO2 and Tinsp by PID

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[12] Even assuming that Patent Owner was correct, *i.e.*, that Taube disclosed a device that would administer a therapy that a person of ordinary skill would immediately recognize was fatal to the patient, such disclosure would not disqualify Taube as prior art. To begin with, nothing in the claims requires a particular level of efficacy or a treatment result. Moreover, under an obviousness analysis, a reference need not work to qualify as prior art; "it qualifies as prior art, regardless, for whatever is disclosed therein." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003). "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989).

control, but argues that "[a]s described with regard to Anderson, the output of a PID controller changes continuously with time and cannot be used to safely adjust PEEP whose effect on patient's oxygenation is not instantaneous." PO Resp. 49. Patent Owner contends that "[u]sing PID controllers to adjust PEEP automatically can be quite hazardous to patients, has not been done in any commercial ventilators, and is not used in any of the embodiments of the Patent," and "[f]or this reason alone, the PTAB should not rely on Taube's disclosure." *Id.* Patent Owner does not provide adequate evidentiary support for this argument.[13] Moreover, even if Patent Owner were correct, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d at 1334 (citing *In re Gurley*, 27 F.3d at 553). Patent Owner fails to explain how PID control would be outside the scope of the language of the claims. Instead, Patent Owner agreed that PID control was within the meaning of "determining" and "calculating." *See* PO Resp. 13; Ex. 1027, 116:25–117:3.

Patent Owner also argues that in Taube, FIO2 is not determined to reduce the difference between measured oxygen level and desired level and PEEP is not controlled to keep ratio of PEEP/FIO2 within a prescribed range. PO Resp. 51–52. Petitioner relies on

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[13] The only evidence in the record that seems to support this argument is in Dr. Tehrani's Declaration. *See* Ex. 2010 ¶ 92. However, Dr. Tehrani provides no citations to support the factual contentions underlying this argument, and the record contains two prior art references—Taube and Anderson—that do describe PID control of PEEP. Thus, we give this testimony little weight.

Carmichael,[14] however, for the specifications of the PEEP and FIO2 control, and relies on Clemmer to show that it would have been a matter of routine programming to implement Carmichael's control of PEEP and FIO2 in Taube's automated ventilator control system. *See* Pet. 66.

As to Clemmer, Patent Owner argues that Clemmer's "protocols" provide for manual adjustment of treatment parameters by physicians, and the adjustments are made several hours apart. PO Resp. 52 (citing Ex. 1008, 26:39–42). Patent Owner also argues that Clemmer does not use a PID control system or closed-loop feedback control. *Id.* at 53, 67.

We disagree with Patent Owner's assertion that Clemmer's protocols require manual adjustment. For instance, Clemmer discusses, with reference to Figure 4, an alternative with continuous monitoring and adjustment. Ex. 1008, 18:53-63. Moreover, Clemmer teaches that "patient instructions can be carried out automatically" and the control programming instructions of the "inventive system therefore accomplished closed loop control of ventilation." Ex. 1008, Abstract, 5:2–3, 9:3–4. Further, whether Clemmer discloses PID control or closed-loop feedback control is not relevant to the asserted ground, which relies on Taube for disclosing these features. Pet. 61-63.

As to the combination, Patent Owner argues that "Carmichael is all about manual adjustments of PEEP and FIO2 several hours apart," and "Taube claims continuous PID control of PEEP and FIO2." PO Resp.

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[14] We addressed above, in our analysis of the other grounds, the scope and content of Carmichael.

69. Patent Owner contends that "combining any of Carmichael, ARDSNET or Clemmer's manual adjustments of parameters would render Taube's PID automatic control of PEEP and FIO2 system inoperable and thus Taube would not operate on the same principles." *Id.* at 74. This argument misstates Petitioner's proposed combination. Petitioner does not propose to modify Taube's automated ventilator control system to use manual adjustments. Rather, Petitioner proposes that it would have been obvious to employ Taube's automated system to implement Carmichael's treatment protocol for adjustment of PEEP and FIO2 in ARDS patients, using routine programming, as evidenced by Clemmer. Pet. 65–66.

Patent Owner contends that "[n]ot only it is impossible to combine these systems, but a desired oxygen level is not definable in Taube, because "Taube maximizes the patient's oxygen level if that level increases." *Id.* at 69. However, as we explained above, *supra* pp. 45–47, this argument is based on Patent Owner's unreasonable interpretation of Taube. *See* Ex. 1029 ¶¶ 13–19. Moreover, Petitioner proposes to modify Taube's treatment regime to implement the treatment regime of Carmichael. Patent Owner never addresses that combination.[15] We have reviewed Petitioner's evidence and find it persuasive that such a

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[15] Patent Owner also argues that we failed to take into account the Examiner's consideration of Taube during prosecution. *See* PO Resp. 47, 67. However, we discussed at length the Examiner's consideration of Taube in our Institution Decision, and we found that the Examiner materially erred in the consideration of Taube. Inst. Dec. 11–22 (explaining the material errors in the Examiner's consideration of Taube). Therefore, we do not find the Examiner's prior consideration of Taube to be entitled to any

combination would have been obvious to a person of ordinary skill at the time of the invention. *See* Pet. 60–66; Ex. 1002 ¶¶ 419–438.

For these reasons, Petitioner has demonstrated, by a preponderance of the evidence, the unpatentability of claim 1, under 35 U.S.C. § 103(a), based on the combined teachings of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi.

7. Analysis of Claim 29

Petitioner relies on the same findings and combination of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, Rossi to challenge method claim 29 as presented for its challenge to claim 1. Pet. 70-72. Patent Owner does not present separate arguments for claim 29. *See* PO Resp. 30-33, 51-54 (presenting the same arguments for claims 1 and 29). We have reviewed Petitioner's evidence and arguments for claim 29, and find them sufficient. *See* Pet. 70–72. Thus, for the same reasons discussed above in our analysis of claim 1, Petitioner has shown by a preponderance of the evidence that claim 29 would have been obvious based on the combined teachings of Taube, Carmichael, and Clemmer.

8. Analysis of Claims 2-6, 9-12, 30-33 and 41

Claims 2-6, 9-12, 30-33, and 41 all depend directly or indirectly from claim 1 or claim 29. We

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weight in determining whether the challenged claims are patentable over the combination of Taube, Carmichael, ARDSNET, Clemmer, and Rossi.

have reviewed Petitioner's cited evidence and explanation regarding why the combination of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi, renders obvious the subject matter of these dependent claims and find the evidence and reasoning sufficient to show by a preponderance of the evidence that these claims are also unpatentable as obvious. Although Patent Owner discusses Rossi in its Patent Owner Response, Patent Owner does not contest Petitioner's reliance on Rossi for its disclosure of measurement of PEEPi (claims 9, 10, 30). PO Resp. 53-54 (arguing that Rossi individually does not describe any system to control a ventilator or to control PEEP, and not presenting arguments against Rossi in combination with the teachings of Taube, Carmichael, and Clemmer).

Patent Owner raises no other arguments regarding these claims other than those considered above with respect to claim 1. We determine that Petitioner has shown by a preponderance of the evidence that Taube, Carmichael, Clemmer, and Rossi renders obvious claims 2-6, 9-12, 30-33, and 41.

H. Remaining Grounds

Having determined that Petitioner establishes by a preponderance of the evidence that the subject matter of claims 1-6, 9-12, 29-33, 41 would have been obvious over the combination of Carmichael, Anderson, Tehrani '268, and Rossi and the combination of Taube, Carmichael, as evidenced by ARDSNET, Clemmer, and Rossi, we do not address Petitioner's additional ground of obviousness based on Carmichael (as evidenced by ARDSNET and Waisel) challenging claims 1, 2, 5, 6, 11, 29, 31-33, 41 (Ground 2). *See SAS*

Inst. Inc. v. Iancu, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) (nonprecedential) ("We agree that the Board need not address [alternative grounds] that are not necessary to the resolution of the proceeding.").

III. Petitioner's Motion to Exclude

Petitioner seeks to exclude Exhibits 2009, 2012, 2013, 2014, 2015, 2018, 2022, 2024, 2025, 2026, and 2027. We grant-in-part, deny-in-part, and dismiss-as-moot-in-part Petitioner's Motion to Exclude.

A. Untimely Exhibits (Exhibits 2022, 2024–2026)

Under 37 C.F.R. § 42.23(b), a "sur-reply may only respond to arguments raised in the corresponding reply and may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness." 37 C.F.R. § 42.23(b). The Consolidated Trial Practice Guide states that a "sur-reply may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness." CTPG, at 73.

Patent Owner filed two declarations with its Sur-Reply: the Third Declaration of Dr. Fleur Tehrani (Ex. 2022) and the Declaration of Dr. James H. Roum (Ex. 2026). Patent Owner contends that these exhibits were necessary because Petitioner's Reply contained new arguments and was, in effect, "a brand-new Petition based on new declarations and evidence." PO Opp. 3. In particular, Patent Owner contends that

Petitioner's construction of "for a next breath" was new and required new evidence to respond. *Id.* at 4. As for Exhibit 2026, Patent Owner argues that Dr. Roum's declaration is necessary to "prevent Petitioner from misleading the Board." *Id.* at 5. In particular, Patent Owner asserts that Dr. Roum's declaration is necessary to respond to Dr. Anderson's and Dr. Imbruce's testimony "regarding the alleged clinical trials in Anderson having been conducted in accordance with a hospital Internal Review Board (IRB) regulations and the FDA rules." *Id.* at 5–6.

We agree with Petitioner that Exhibits 2022 and 2026 are untimely and should be excluded. Rule 42.23(b) and the Consolidated Trial Practice Guide are clear that such declarations cannot be filed with a sur-reply. There is no automatic "responding to new arguments" exception to that prohibition. As the Consolidated Trial Practice Guide explains, the proper course if new arguments were presented in the Reply would be to seek authorization to file a motion to strike. CTPG, 80–81. Patent Owner did not do that. Regardless, our rules do not permit a party to file exhibits without authorization. 37 C.F.R. § 42.7(a) (forbidding filings not authorized); § 42.23(b) (forbidding new evidence other than deposition transcripts with a sur-reply). Our rules only authorize limited exhibits that may be filed with a sur-reply. *See* 37 C.F.R. § 42.23(b). Patent Owner did not seek authorization to file these additional exhibits.

Moreover, we disagree with Patent Owner that the interests of justice support allowing these declarations. First, Patent Owner's contention that Petitioner's challenge to Dr. Tehrani's credentials requires a

response is not persuasive. Petitioners routinely challenge the credentials of experts. Dr. Tehrani has testified at length about her credentials in her first two declarations and has provided a curriculum vitae and other materials that will allow us to assess them. Dr. Tehrani was also allowed to testify to her credentials in her deposition and her counsel could have asked her additional questions on re-direct. We see no need for additional testimony from either Dr. Tehrani or Dr. Roum on that matter. Second, as for the disputes regarding the Anderson reference, we explained above why Patent Owner's arguments about FDA authorization and the intricacies of clinical trials were not persuasive. Patent Owner's new testimony simply repeats the same assertions and does not add anything new that would change that conclusion. Therefore, that testimony is also unnecessary. Finally, with respect to the alleged new claim construction, we disagree with Patent Owner that the claim construction is new or that additional expert testimony on the claim construction that was already thoroughly discussed in Patent Owner's prior declarations will add any further illumination to this subject. Moreover, we have found that the claim constructions make no difference to the result on Grounds 3 and 4, which also render this testimony unnecessary. Accordingly, because they were filed in violation of our rules and the interests of justice do not support excusing that violation, we grant Petitioner's Motion to Exclude Exhibits 2022 and 2026.

In addition to the declarations discussed above, Patent Owner also filed Exhibits 2024 and 2025 with its Sur-Reply. Exhibit 2024 is an article entitled "What You Need to Know About Brain Oxygen

Deprivation," which was published in 2021. Ex. 2024. Patent Owner cited Exhibit 2024 to address how the term "oxygen deprivation" would have been understood at the time of the invention of the '571 patent. Sur-Reply 15. Patent Owner argues that this article is necessary to address the "next breath" dispute. PO Opp. 13–14. Exhibit 2025 is a definition of "trial and error" from the Merriam-Webster Online Dictionary. Patent Owner argues that this exhibit is necessary to respond to alleged new arguments in the Reply. *Id.* at 14.

We agree with Petitioner that these exhibits are also untimely and should be excluded. We are also not persuaded that the interests of justice require us to allow these exhibits. With respect to Exhibit 2024, we fail to see why an article on oxygen deprivation, at a very general level, is necessary for this proceeding given that there seems to be no dispute about the need to prevent oxygen deprivation. As for Exhibit 2025, we do not believe that a dictionary definition of the common expression "trial and error," a term not found in the claims of the '571 patent, is necessary for this proceeding. Accordingly, because they are untimely and the interests of justice would not be served by allowing them to be admitted, we grant Petitioner's Motion to Exclude Exhibits 2024 and 2025.

B. Exhibits 2009, 2018, and 2027

Exhibit 2009 is The Opinion of the United Kingdom Intellectual Property on Infringement of the GB2423721 Patent, Opinion #09/18, issued on June 6, 2018. Ex. 2009, 1. Exhibit 2018 is several pages from the textbook *Mechanical Ventilation* by Neil R.

MacIntyre and Richard D. Branson. Exhibit 2027 purports to be an email between an employee of the UK Intellectual Property Office and Dr. Tehrani. Ex. 2027, 1. Petitioner argues that these exhibits should be excluded. Pet. Mot. 3–5, 9–10, 12; Pet. Opp. 10–11. We did not rely on Exhibits 2009, 2018, and 2027 in reaching our decision in this case because Patent Owner does not cite them in making any arguments regarding patentability or, as to Exhibit 2018, which as with Exhibit 2007 and 2012 discusses assist/control mode ventilation, they are cumulative of other exhibits discussed. Therefore, we dismiss Petitioner's Motion to Exclude Exhibits 2009, 2018, and 2027 as *moot*.

C. Exhibits 2012–2015

Exhibit 2012 is purportedly a website entitled "Ventilation Modes and Monitoring." Ex. 2012. Exhibit 2013 appears to be portions of a chapter of a book entitled "Digital Control System Analysis & Design," by Charles L. Phillips et al. Ex. 2013, 1. Exhibit 2014 is an information sheet from the U.S. FDA's website. Ex. 2014, 1. Exhibit 2015 is an Investigational Device Exemption (IDE) form printed from the U.S. FDA's website. Petitioner argues that these exhibits are irrelevant and should be excluded under Fed. R. Evid. 401–403. Pet. Mot. 4–5. Petitioner also contends that Exhibits 2012, 2014, and 2015 should be excluded under Fed. R. Evid. 901–902.

Here, Patent Owner does rely on these exhibits to support its arguments. We find this sufficient to clear the very low bar of relevance. *See United States v. Whittington*, 455 F.3d 736, 739 (6th Cir. 2006) ("[T]he district court correctly noted that the relevance threshold is very low under Rule 401.") (internal quotation

marks omitted). As for Fed. R. Evid. 403, assuming that it applies in these non-jury proceedings, *Schultz v. Butcher*, 24 F.3d 626, 632 (4th Cir. 1994) (finding court should not exclude evidence under Rule 403 in non-jury trial on grounds of unfair prejudice), we find that Petitioner's arguments deal not with prejudice, but rather, the weight we should give the evidence.

As for authentication, documents are authenticated by evidence "sufficient to support a finding that the item is what the proponent claims it is." Fed. R. Evid. 901(a). Authenticity is, therefore, not an especially high hurdle for a party to overcome. *See United States v. Patterson*, 277 F.3d 709, 713 (4th Cir. 2002); *see also United States v. Ceballos*, 789 F.3d 607, 617–18 (5th Cir. 2015) (noting "low" burden for authentication); *United States v. Isiwele*, 635 F.3d 196, 200 (5th Cir. 2011) (noting flaws in authentication go to weight not admissibility). Patent Owner's counsel has offered a declaration attesting to the accuracy of these documents. *See* Ex. 2019 ¶¶ 3–5. We find this testimony sufficient to clear the low bar for authentication. Accordingly, we deny Petitioner's Motion to Exclude Exhibits 2012–2015.

D. Summary

Accordingly, for the reasons above, we grant Petitioner's Motion to Exclude Exhibits 2022, 2024–2026, dismiss-as-moot Petitioner's Motion to Exclude Exhibits 2009, 2018, and 2027, and deny Petitioner's Motion to Exclude Exhibits 2012–2015.

IV. Patent Owner's Motion to Exclude

Patent Owner moves to exclude Exhibits 1002, 1005, 1011, 1013, 1023, 1024, 1025, 1026, 1028, and

1029. We consider each of these exhibits in turn. For the following reasons, we deny-in-part and dismiss-as-moot-in-part Patent Owner's Motion to Exclude.

A. Exhibit 1002

Exhibit 1002 is the First Declaration of Dr. Richard Imbruce. Patent Owner argues that Dr. Imbruce's experience is distant from the '571 patent and not up to date. PO Mot. 3–4. Patent Owner contends that "Exhibit 1002 presents numerous incorrect, and totally unsubstantiated allegations about the prior art and the Patent." *Id.* at 4. Patent Owner asserts that "Dr. Imbruce, has offered expert testimony on matters outside his knowledge in the past. The Patent Owner brought to the attention of the Board that Dr. Imbruce had to be disqualified in another case (Ex. 2017) (POR, 75-77), because he had offered incorrect testimony not within his expertise as admitted by the Petitioner (PRPOR at 23)." *Id.* at 5. Patent Owner also argues that Dr. Imbruce failed to bring "to the attention of the Board that two of the Petitioner's alleged prior art, Ex. 1011 and Ex. 1013, both non-reviewed papers, do not present true data as explained by the Patent Owner." *Id.* Patent Owner submits that "Ex. 1002 is a large collection of flawed and unsubstantiated allegations that has caused an unjustified institution in this case." *Id.* at 6. Patent Owner "requests the exclusion of this evidence because it is totally misleading and prejudicial (FRE 401-403), is not based on sufficient facts or data and the expert has not reliably applied the principles and methods to the facts of the case (FRE 702) and is not based on evidence (FRE 901)." *Id.*

Petitioner opposes, pointing to the relevant experience in Dr. Imbruce's curriculum vitae and that the experiences he testified about in his deposition. Pet. Opp. 1 (citing Ex. 1003; Ex. 2016, 10:23–12:22).

Patent Owner's arguments go to the weight we should give Dr. Imbruce's testimony, not its admissibility. *See Microfinancial, Inc. v. Premier Holidays Int'l.*, 385 F.3d 72, 81 (1st Cir. 2004) ("When the factual underpinning of an expert's opinion is weak, it is a matter affecting the weight and credibility of the testimony—a question to be resolved by the [factfinder]."). The prior case where Dr. Imbruce's testimony was excluded (Ex. 2017) involved a very narrow and specialized area (failure analysis of a particular specialized medical device—a heart-lung machine). Patent Owner's arguments do not persuade us that we should exclude Dr. Imbruce's testimony. There need not be a perfect match between the expert's qualifications and the patent at issue. *See SEB S.A.*, 594 F.3d at 1373. It is not necessary for Dr. Imbruce to demonstrate that he spent the bulk of his career personally designing mechanical ventilators. Indeed, to testify as an expert under Fed. Rule Evid. 702, a person need not be one of ordinary skill, but may be "qualified in the pertinent art." *See B/E Aerospace, Inc. v. MAG Aerospace Indus. LLC*, Paper 104 at 13–14 (Final Written Decision) (declining to exclude the testimony of expert witness that lacked hands-on experience with the claimed subject matter). We agree with Petitioner that Dr. Imbruce's lengthy experience, including a) developing ventilator devices and work on a portable oxygen generator to provide emergency care to patients undergoing respiratory distress (Ex. 1003, Rapid Oxygen Company work; Ex. 2016, 10:23–12:22); (b) "developing clinical

protocols for new modalities in artificial ventilation" in the relevant 2003– 2009 time period of the patent at issue in this IPR; (c) "laboratory and clinical research funded by DOD developing oxygen delivery therapies to treat hemorrhagic shock in wounded soldiers" in the 2009–2016 time period (Ex. 1003); and (d) ongoing design and use of ventilators, provides him sufficient experience and knowledge of the claimed subject matter for his opinion to remain of record. Ex. 1003; Ex. 2016, 10:23–12:22.

Moreover, "[t]he policy considerations for excluding expert testimony, such as those implemented by the gatekeeping framework established by the Supreme Court in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), are less compelling in bench proceedings such as inter partes reviews than in jury trials." *Nestle Healthcare Nutrition, Inc. v. Steuben Foods, Inc.*, IPR2015-00249, Paper 76 at 23 (PTAB June 2, 2016). To be sure, we take into account the qualifications of an expert witness—and any shortcomings revealed through cross-examination—when evaluating the weight to be given that witness's testimony. But the wholesale exclusion of a witness's declarations is rarely called for in a proceeding before the Board. We have considered Dr. Imbruce's qualifications in determining the weight to be given his testimony.

Patent Owner's other objections are without merit. Fed. R. Evid. 901 has no application here—there is no doubt that Dr. Imbruce's declaration is authentic. Nor can there any doubt that it is relevant under Fed. R. Evid. 401. *See Whittington*, 455 F.3d at 739 ("[T]he district court correctly noted that the relevance threshold is very low under Rule 401.") (internal quotation marks omitted). As for Fed. R. Evid. 403, assuming

that it applies in these non-jury proceedings, *Schultz*, 24 F.3d at 632 (finding court should not exclude evidence under Rule 403 in non-jury trial on grounds of unfair prejudice), we find that Patent Owner's arguments deal not with prejudice, but rather, the weight we should give the testimony. Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1002.

B. Exhibit 1005

Patent Owner argues that we should exclude the Taube patent under Federal Rules of Evidence 401–403. PO Mot. 6. In particular, Patent Owner argues that it was "raised by the Examiner" and "was fully responded to before the Patent was allowed" and "cannot be combined with any manual chart or table" and is "detrimental" and "[a] Patent describing a detrimental method should not be used at any trial because it is misleading, irrelevant to the facts and prejudicial." *Id.*

We agree with Petitioner that Patent Owner's arguments fail to provide any basis for excluding evidence under Federal Rules of Evidence 401–403. *See* Pet. Opp. 2, 4–6. Federal Rule of Evidence 401 provides that evidence is relevant if it "has any tendency to make a fact more or less probable than it would be without the evidence" and "the fact is of consequence in determining the action." Fed. R. Evid. 401; Fed. R. Evid. 402 ("Relevant evidence is admissible"). Courts have characterized the relevance threshold as being "very low." *United States v. White*, 692 F.3d 235, 246 (2d Cir. 2012) (quoting *United States v. Al-Moayad*, 545 F.3d 139, 176 (2d Cir. 2008)). The fact that Taube was considered by the Examiner does not negate its relevance or admissibility. Similarly, the argument

about whether Taube can be combined goes to the merits of the combination, not the admissibility of the evidence, because although the combination might not be obvious, the evidence would still be relevant. Finally, Patent Owner's arguments that Taube is not relevant because of the alleged detrimental nature of Taube—*i.e.*, that Taube allegedly discloses a device that will increase and decrease oxygen levels in a way that is harmful (*see supra* pp. 45–46) are also unpersuasive. *See* PO Mot. 6; PO Reply 2. Under an obviousness analysis, a reference need not work to qualify as prior art; "it qualifies as prior art, regardless, for whatever is disclosed therein." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003). "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). Thus, even if Patent Owner's arguments regarding the operation of Taube were correct, which as we explain above they are not, *see supra* pp. 45–46, it would not be basis for excluding Exhibit 1005. Instead, we find that Exhibit 1005 easily clears the very low threshold of relevance.

Patent Owner's argument that Federal Rule of Evidence 403 compels exclusion is equally unavailing. PO Mot. 6; PO Reply 2. Rule 403 has limited applicability, if any, to bench trials like this proceeding. *See, e.g., Schultz*, 24 F.3d at 632 (holding that "in the context of a bench trial, evidence should not be excluded under 403" because the court can "hear relevant evidence, weigh its probative value and reject any improper inferences"). In the end, Patent Owner's arguments simply go to the weight the evidence should be given and not its admissibility. Accordingly,

we deny Patent Owner's Motion to Exclude Exhibit 1005.

C. Exhibit 1011

Patent Owner argues that Exhibit 1011, Waisel, should be excluded because it "does not present true data" and it is "misleading, presents unreliable data, is irrelevant to the facts and prejudicial." PO Mot. 7; PO Reply 2–3. Again, even if Patent Owner's assertions are correct, under an obviousness analysis, a reference need not work to qualify as prior art; "it qualifies as prior art, regardless, for whatever is disclosed therein." *Amgen*, 314 F.3d at 1357. Moreover, Patent Owner's assertions that Waisel does not present true data are based on speculation and are not persuasive. In addition, as we explained above, Patent Owner's contentions that Waisel cannot be considered because it does not disclose an FDA Investigational Device Exception is not persuasive. *See supra* pp. 34–35 (explaining with respect to Anderson why similar contentions were not persuasive). Patent Owner also argues Waisel should be excluded under Federal Rule of Evidence 702 (PO Mot. 7), but that rule relates to expert testimony, which this prior art reference is not. Finally, we find that Petitioner has provided more than sufficient evidence to authenticate Waisel (*see* Ex. 1017 ¶¶ 77– 84, 120), so Patent Owner's authentication objection (PO Mot. 7) is not persuasive. Accordingly, for similar reasons as we articulated for Exhibit 1005, we deny Patent Owner's Motion to Exclude Exhibit 1011.

D. Exhibit 1013

Patent Owner argues that Exhibit 1013, the Anderson reference, should be excluded "because it presents misleading and unreliable data, is irrelevant to the facts and prejudicial ((FRE 401-403), is not based on reliable facts and data (FRE 702), and is not based on evidence (FRE 901)." PO Mot. 8. For the reasons stated above for Exhibits 1005 and 1011, these arguments with respect to Federal Rules of Evidence 401–403 and 702 are not persuasive. As for Patent Owner's objection under Federal Rule of Evidence 901, Petitioner has provided more than sufficient evidence that Exhibit 1013 is what it purports to be, *i.e.*, a copy of the Anderson reference. *See, e.g.*, Ex.1017 ¶¶ 94–101, 120; Ex. 1028 ¶¶ 3–5. Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1013.

E. Exhibits 1023–1025

Patent Owner seeks to exclude Exhibits 1023–1025, which are three exhibits relating to the Terumo Advanced Perfusion System. *See* Exs. 1023– 1025. Patent Owner's declarant was questioned on these exhibits at her deposition, but neither party cites or discusses these exhibits. We did not rely on these exhibits in reaching our decision, so we dismiss Patent Owner's Motion to Exclude Exhibits 1023–1025 as *moot*.

F. Exhibit 1026

Exhibit 1026 s a United Kingdom Intellectual Property Office UK IPO Opinion dated March 19, 2021, regarding invalidity of a UK Patent No. GB 2423721, a parallel UK patent to the US Patent at

issue in this proceeding. Patent Owner argues that we should exclude Exhibit 1026 because it is "a non-binding, non-final opinion from another jurisdiction that is presently under review and thus is completely irrelevant to the facts and prejudicial (FRE 401–403) is not based on evidence (FRE 901), and was relied upon for the first time in Petitioner's Reply." PO Mot. 2. We did not rely on Exhibit 1026 in reaching our decision in this case. Therefore, we dismiss Patent Owner's Motion to Exclude Exhibit 1026 as *moot*.

G. Exhibit 1028

Patent Owner argues that Exhibit 1028, the Declaration of Dr. Jeffrey R. Anderson, P.E., should be excluded because "it is irrelevant to the facts and prejudicial (FRE 401 – 403), is inadmissible hearsay (FRE 801), is not based on sufficient facts or data (FRE 702), is not based on substantiated evidence (FRE 901), and was relied upon for the first time in Petitioner's Reply." PO Mot. 13–14. None of these arguments is persuasive. First, Federal Rule of Evidence 702 does not apply because Dr. Anderson is not offered as an expert witness, but instead as a fact witness based on his firsthand knowledge. *See* Pet. Opp. 8. Second, Patent Owner provides no explanation of how Dr. Anderson's testimony is hearsay (under Federal Rule of Evidence 801) or how it is not authentic under Federal Rule of Evidence 901. *See id.*; PO Mot. Reply 5. Federal Rule of Evidence 801(c) defines "hearsay" as "a statement that: (1) the declarant does not make while testifying at the current trial or hearing; and (2) a party offers in evidence to prove the truth of the matter asserted in the statement." Here, Dr. Anderson's declaration is *testimony offered in the current trial*, and is, therefore, by definition *not*

hearsay. Thus, Patent Owner's blanket hearsay objection against the entire declaration is without merit. As for Federal Rule Evidence 901, that rule deals with authentication. *See* Fed. R. Evid. 901. There is no dispute that Dr. Anderson's declaration is what it purports to be—*i.e.*, the declaration of Dr. Jeffrey Anderson. A Rule 901 objection has no place here. To the extent that Patent Owner means Federal Rule of Evidence 602, which requires that a witness have personal knowledge in order to testify as a fact witness, Dr. Anderson, as one of the named authors of the paper in question has shown that he has the requisite personal knowledge to testify. *See* Ex. 1028 ¶¶ 3–22 (explaining his personal knowledge of the events on which he testifies).

Finally, Patent Owner's arguments regarding relevance (Fed. R. Evid. 401), prejudice (Fed. R. Evid. 403), and the alleged lateness of the exhibit are not persuasive. Patent Owner argued extensively in the Patent Owner Response with supporting testimony in her First and Second Declarations and in the Patent Owner Response that Dr. Anderson's paper was false and the reported trial never occurred. *See* PO Resp. 37–41, 60–63. Petitioner was entitled to respond in its Reply to the arguments that Patent Owner made. *See* 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition, patent owner preliminary response, patent owner response, or decision on institution."). Our rules allow that response to be supported by new evidence. *See id.* (only limiting the evidence that may be filed with a sur-reply). We find that Dr. Anderson's testimony is not new, but is directly responsive to Patent Owner's own arguments and accusations of misrepresentation

attributed to Dr. Anderson and his co-authors. Thus, we agree with Petitioner that Dr. Anderson's testimony is relevant and timely. As for Patent Owner's prejudice argument, Patent Owner does not offer a credible explanation as to any prejudice that arises from Dr. Anderson's testimony that seeks to refute the argument made by Patent Owner that Dr. Anderson misrepresented data in his 1994 paper. Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1028.

H. Exhibit 1029

Patent Owner seeks to exclude Exhibit 1029, the Second Declaration of Dr. Richard Imbruce. PO Mot. Exclude 14. Patent Owner argues that "Dr. Imbruce makes numerous unsubstantiated and incorrect allegations in this declaration and therefore, Ex. 1029 is irrelevant and prejudicial (FRE 401-403)." *Id.* Patent Owner further contends that Dr. Imbruce's second declaration should be excluded because it relies on other exhibits Patent Owner has sought to exclude. *Id.* Patent Owner also argues that "Dr. Imbruce even signs his name as RRT (*i.e.*, Registered Respiratory Therapist) despite that he has not practiced respiratory therapy or renewed his RT certificate for 40 years." *Id.*

Patent Owner additionally seeks to exclude Exhibit 1029 because Patent Owner contends that "Petitioner is requesting a new claim construction for 'a next breath of the patient,' and is providing new arguments on Waisel." *Id.* Patent Owner requests that Exhibit 1029 be excluded in its entirety, or alternatively, that the portions of Exhibit 1029 referring to the new claim

construction be excluded, which appear to be paragraphs 22–28 of Exhibit 1029. *Id.*

Petitioner responds that Dr. Imbruce's testimony does not offer a new claim construction, *but see*ks to respond to Patent Owner's arguments and the Institution Decision's preliminary findings regarding Waisel. Pet. Opp. 9–10. Thus, Petitioner contends that the testimony is proper.

We agree with Petitioner that Patent Owner's request to exclude Exhibit 1029 should be denied. To begin with, an expert may rely on otherwise inadmissible evidence in forming his or her opinion. Thus, even if Dr. Imbruce relied on some exhibits that are inadmissible, it would not necessarily warrant excluding his testimony. *See* Fed. R. Evid. 703. Moreover, as we found above, Patent Owner's objections to the exhibits relied on by Dr. Imbruce are without merit, so we find unavailing the argument that Dr. Imbruce relied on excluded evidence. Furthermore, Patent Owner's arguments concerning Dr. Imbruce's title and experience go to the weight we should give Dr. Imbruce's testimony, not its admissibility. *See Microfinancial, Inc.*, 385 F.3d at 81 ("When the factual underpinning of an expert's opinion is weak, it is a matter affecting the weight and credibility of the testimony—a question to be resolved by the [factfinder]."). Patent Owner was free to cross examine Dr. Imbruce on these points, which it has. Finally, as for the allegedly new arguments, we begin by noting that a motion to exclude is not the proper vehicle to seek to strike new arguments. *See* CTPG, at 79 ("Nor should a motion to exclude address arguments or evidence that a party believes exceeds the proper scope of reply or surreply."). In any event, the allegedly new arguments in

paragraphs 20–28 are not a basis for excluding the entirety of Exhibit 1029. As for paragraphs 20– 28, we have reviewed them and agree with Petitioner that they are not new arguments, but instead, respond directly to the Decision to Institute and the arguments Patent Owner has made in this proceeding. Accordingly, we deny Patent Owner's Motion to Exclude Exhibit 1029.

V. Conclusion[16]

After considering all the evidence and arguments presently before us, we determine Petitioner has established by a preponderance of the evidence that the challenged claims are unpatentable.

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16 Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

In summary,

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1, 2, 5, 6, 11, 29, 31-33, 41	102	Carmichael		1, 2, 5, 6, 11, 29, 31–33, 41
1, 2, 5, 6, 11, 29, 31-33, 41	103(a)	Carmichael (as evidenced by ARDS-NET and Waisel) [17]		
1-6, 9-12, 29-33, 41	103(a)	Carmichael, Anderson, Tehrani '268, Rossi	1-6, 9-12, 29-33, 41	
1-6, 9-12,	103(a)	Taube, Carmichael, ARDSNET, Clemmer, Rossi	1-6, 9-12, 29-33, 41	

[17] This ground was not reached. *See supra* § II.H.

Overall Outcome	1-6, 9-12, 29-33, 41	

We grant-in-part, deny-in-part, and dismiss-as-moot-in-part Petitioner's Motion to Exclude. We deny-in-part and dismiss-as-moot-in-part Patent Owner's Motion to Exclude.

VI. Order

For the reasons given, it is:

ORDERED, that Petitioner *has shown* based on a preponderance of evidence, that claims 1-6, 9-12, 29-33, and 41 of U.S. Patent 7,613,649 B2 are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is *granted-in-part, denied-in-part,* and *dismissed-as-moot-in-part*;

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied-in-part* and *dismissed-in-part*; and

FURTHER ORDERED because this is a final written decision, the parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FOR PETITIONER:

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ORDER DENYING PETITION FOR REHEARING, UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT (AUGUST 23, 2023)

Note: This order is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

FLEUR TEHRANI,

Appellant,

v.

HAMILTON TECHNOLOGIES LLC,

Appellee.

No. 2022-1732

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2020-01199.

Before: MOORE, Chief Judge, NEWMAN, LOURIE, DYK, PROST, REYNA, TARANTO, CHEN, HUGHES, STOLL, CUNNINGHAM, and STARK, Circuit Judges.

PER CURIAM.

Fleur Tehrani filed a combined petition for panel rehearing and rehearing en banc. The petition was

referred to the panel that heard the appeal, and thereafter the petition was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue August 30, 2023.

FOR THE COURT

/s/ Jarrett B. Perlow
Clerk of Court

Date: August 23, 2023

TEHRANI, F. T., *AUTOMATIC CONTROL OF MECHANICAL VENTILATION. PART 1: THEORY AND HISTORY OF THE TECHNOLOGY*, JOURNAL OF CLINICAL MONITORING AND COMPUTING, VOL. 22, PP. 409-415, 2008

JOURNAL OF CLINICAL MONITORING AND COMPUTING

Automatic Control of Mechanical Ventilation. Part 1: Theory and History of the Technology

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Tehrani FT. Automatic control of mechanical ventilation. Part 1: theory and history of the technology.

J Clin Monit Comput 2008; 22:409–415

ABSTRACT. Objective. In this article, automatic control technology as applied to mechanical ventilation is discussed and the techniques that have been reported in the literature are reviewed. Methods. The information in the literature is reviewed and various techniques are compared. Results. Automatic control

has been applied in many ways to mechanical ventilation since several decades ago. More aggressive techniques aimed at automatic and more optimal control of the main outputs of the machine have emerged and continue to be enhanced with time. Conclusions. Development of more efficient automatic techniques and/or enhancement of the present methods are likely to be pursued to make this technology more compatible with future healthcare requirements.

KEY WORDS. mechanical ventilation, automation, closed-loop control.

Introduction

Closed-loop automatic techniques have been used in various forms in mechanical ventilation for several decades. The older technologies are mostly concerned with provision of a set volume and/or pressure of gas to the patient at a prescribed rate by the clinician. Correct delivery of the set volume/pressure of the inspiratory gas to the patient necessitates closed-loop monitoring of the delivered values to the patient by the machine. Modalities that embody mandatory minute volume technique (MMV) [1], various closed-loop technologies such as synchronized intermittent mandatory ventilation (SIMV), along with many variations of such modalities have been developed and used to assure delivery of a determined volume of gas to the patient in concert with his/her spontaneous breathing activity. Newer technologies utilize more aggressive methods directed at automatic control of the main outputs of ventilators in response to patient's

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1 Hewlett AM, Platt AS, Terry VG. Mandatory minute volume. Anesthesia 1977; 32: 163–169.

changing requirements. The controlled outputs in these techniques include volume or pressure of the inspiratory gas, frequency of respiration, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FIO2).

The objective of this article is to discuss closed-loop control as applied to mechanical ventilation, provide an overview of the techniques developed to date, and to assess the direction and trend of this technology in view of the present and future clinical requirements.

Methods

What is closed-loop control?

In a closed-loop control system, the output(s) are controlled based on the present input(s) and previous output(s) and/or state variables of the system. Simply put, in a closed-loop system, some state variables and/or outputs are used to control the next output(s) of the system through feedback loops. A schematic diagram of a closed-loop control system is shown in Figure 1. In this configuration, if "controller inputs" are obtained by adding "reference inputs" to "feedback signals," the system is said to be controlled by positive feedback, and if "feedback signals" are subtracted from "reference inputs" to obtain "controller inputs," the type of feedback is said to be negative. Negative feedback systems can be designed to be stable, while positive feedback systems are inherently unstable.

Closed-loop control as applied to mechanical ventilation

If the concept of feedback as shown in the schematic diagram of Figure 1, is applied to mechanical

ventilation, the "reference inputs" will be the settings provided by the clinician, "Controller" is normally a microprocessor that calculates the next control signal levels, "Actuators" are the circuits and components that receive the Controller's outputs and transform them into actuating signals to effect the pressure applied to the patient airways, and "Plant" is the patient. "Transducers" are sensors and monitors that measure volume, flow, pressure, or blood gas pressures of the patient and produce feedback signals that are in turn used to change the next inputs to the Controller. By this general definition, whenever, any parameter of the Plant (which is the patient) is measured and a signal indicative of that measurement is automatically fed back to the system input, closed-loop control is performed. Therefore, in any volume control mode where the volume of gas delivered

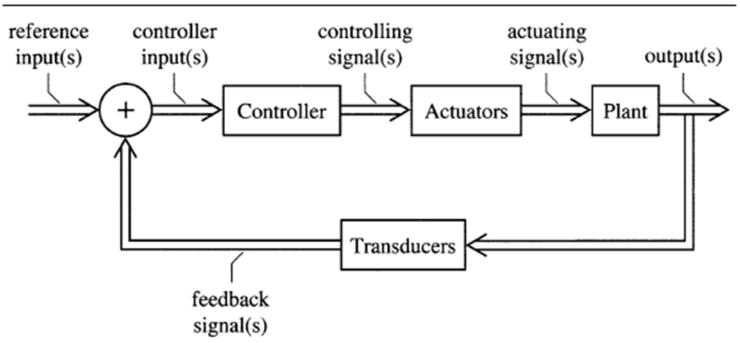

Fig. 1. A schematic diagram of a closed-loop system.

to the patient's airway is measured and adjusted to remain at a prescribed level, or any pressure control mode in which the pressure in the patient's airway is adjusted by the machine, closed-loop control exists. Commonly used ventilation modes such as volume control (VC), pressure control (PC), SIMV, pressure

support (PS), volume support (VS), etc., can be all regarded as closed-loop techniques by this general definition. In control of respiration, the actuating signals can be used to control patient's breathing on a breath-by-breath basis (*i.e.* interbreath control), or adjust the patient's breath during the breathing interval (*i.e.* intrabreath control).

As an example, in a mode called volume-assured pressure support, once a breath is triggered either by the patient or by the machine, the first portion of the breath which is pressure limited is delivered. Then the controller determines whether the target tidal volume is reachable, and if not, inspiration is continued according to peak flow setting to assure the delivery of the required amount of breathing gas. This mode represents an intrabreath, dual closed-loop control technique of breathing. Another example of intrabreath control is PS (or PSV) mode in which gas flow is controlled during the breath to provide pressure support to the patient. An example of closed-loop interbreath control is the pressure regulated volume control (PRVC) mode in which the inspiratory pressure applied by the machine is adjusted based on the patient's measured respiratory dynamic compliance to deliver a target tidal volume of gas to the patient.

Therefore, many modern ventilation techniques can be regarded as closed-loop control methods from an engineering standpoint, but with various degrees of automation.

Closed-loop categories

The application of closed-loop techniques in mechanical ventilation is significantly enhanced if the machine takes over more critical aspects of treatment

by using automatic control. For example, the machine can measure some of the patient's physiological parameters and automatically adjust its main outputs such as tidal volume, inspiratory pressure, or respiratory rate based on the patient's changing requirements. In other words, the ventilator determines some or all of the main targets of breathing through automatic control rather than the clinician. In that case, mechanical ventilation takes on a new dimension of automation.

Among various systems developed for control of mechanical ventilation, there are rule-based systems in which patient parameters such as airway pressure, spontaneous tidal volume and breathing rate, and end-tidal

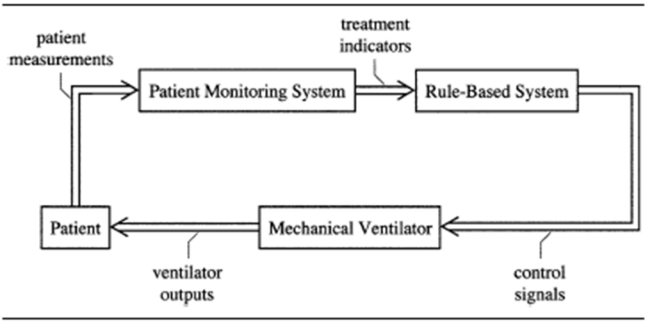

Fig. 2. A schematic block diagram of a rule-based controller.

partial pressure of carbon dioxide (PetCO2) are used as indicators for adjustment of the ventilator's outputs. Figure 2 shows the schematic block diagram of such a system. The control schemes of these rule-based systems that will be described later in this article are based on clinical guidelines and protocols. Although the principles of operation of such systems

can be Compared to those of negative or positive feedback control systems, but they may not be regarded as feedback controlled from an engineering standpoint. In these methods, the patient's measured parameters are not used to formulate the inputs to the system and generate feedback signals to be added to or subtracted from reference inputs as shown in the diagram of Figure 1. Rather, the patient's measured parameters in these systems are used as indicators on whether some incremental changes should be made to the ventilator's output or not.

Based on the above-mentioned differences among mechanical ventilation technologies, closed-loop ventilation as discussed in this article is classified under three main categories:

1. The main ventilatory targets such as tidal volume, respiratory rate, PEEP, FIO2, and the inspiratory pressure are set by the clinician and closed-loop control is used to deliver those targets.
2. Some of the ventilatory targets are periodically adjusted incrementally by the ventilator based on treatment protocols.
3. Some or all of the main ventilatory targets are computed by the ventilator and adjusted through feedback control based on formulations using ventilatory as well as patient parameters, either continuously or periodically.

The features of systems belonging to the 1st category are discussed in some detail elsewhere [2, 3] and are not the focus of this article. The discussions that follow concentrate on the 2nd and 3rd categories above. Those systems will be collectively referred to as "automatic systems." The term "closed-loop" as used in the proceeding sections denotes systems that belong to the 3rd category above. The systems in the 2nd category are identified as "protocol-driven systems."

Overview of Automatic Systems

The first closed-loop system for mechanical ventilation was introduced in 1950s [4], in which the end-tidal PCO2 (PetCO2) was used to control the amount of ventilation provided by the machine. In the next few decades, a series of closed-loop techniques were developed in which PetCO2 or the volume of expired CO2 was measured and used to control the

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2 Branson RD, Johannigman JA, Campbell RS, Davis K Jr. Closed-loop mechanical ventilation. Respir Care 2002; 47: 427–451.

3 Chatburn RL. Classification of ventilator modes: Update and proposal for implementation. Respir Care 2007; 52: 301–323.

4 Saxton GA Jr, Myers G. A servomechanism for automatic regulation of pulmonary ventilation. J Appl Physiol 1957; 11: 326–328.

amount of ventilation given by the machine [5 6 7 8]. The arterial pH level was used next in another closed-loop system to control mechanical ventilation [9]. With the development of microprocessors, a system which incorporated proportional-integral-derivative control (PID) using PetCO2 was introduced in 1982 [10]. This was followed by another microprocessor-controlled system using the PID technique which controlled the rate and tidal volume of breaths based on PetCO2 monitoring [11]. The next system was a closed-loop computer-controlled system for anesthetic delivery and automatic control of ventilation [12]. In this

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5 Frumin MJ, Bergman NA, Holaday DA. Carbon dioxide and oxygen blood levels with a carbon dioxide controlled artificial respirator. Anesthesiology 1959; 20: 313–320.

6 Mitamura Y, Mikami T, Sugawara H, Yoshimoto C. An optimally controlled respirator. IEEE Trans Biomed Eng 1971; BME-18: 330–338.

7 Coles JR, Brown WA, Lampard DG. Computer control of respiration and anesthesia. Med Biol Eng 1973; 11: 262–267.

8 Mitamura Y, Mikami T, Yamamoto K, Kimura M. A dual control system for assisting respiration. Med Biol Eng 1975; 13: 846–854.

9 Coon RL, Zuperku EJ, Kampine JP. Systemic arterial blood pH servocontrol of mechanical ventilation. Anesthesiology 1978; 49: 201–204.

10 Ohlson KB, Westenskow DR, Jordan WS. A microprocessor based feedback controller for mechanical ventilation. Ann Biomed Eng 1982; 10: 35–48.

11 Chapman FW, Newell JC, Roy RJ. A feedback controller for ventilatory therapy. Ann Biomed Eng 1985; 13: 359–372.

12 Ritchie RG, Ernst EA, Pate BL, Pearson JD, Sheppard LC.

system, a PID controller was used to adjust ventilation based on PCO2 monitoring.

Up-to this point, either arterial PCO2 or pH, measured directly or indirectly, was the main variable used to control ventilation. However, using only one variable in control of ventilation is un-natural, can be misleading, and may mask respiratory problems. In 1991, a system was introduced which used multiple patient data to control the rate and tidal volume of breaths of a mechanically ventilated patient [13,14]. In this technique, a modified version of an equation which was based on a hypothesis in physiology presented in 1950 [15], was used to compute the optimal frequency of mechanical ventilation. The closed-loop system in the patented technique [13] was designed to regulate blood gases and used respiratory mechanics data to minimize the work rate of breathing. This system was designed to reduce the load on the respiratory muscles, mimic natural breathing, stimulate spontaneous breathing, and reduce weaning time. Shortly after the patent describing this invention was published in 1991, Hamilton Medical, a ventilator manufacturing company, contacted and subsequently

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Closed-loop control of an anesthesia delivery system: Development and animal testing. IEEE Trans Biomed Eng 1987; 34: 437–443.

13 Tehrani FT. Method and apparatus for controlling an artificial respirator. US Patent No. 4,986,268, issued January 22, 1991.

14 Tehrani FT. Automatic control of an artificial respirator. Proc IEEE EMBS Conf 1991; 13: 1738–1739.

15 Otis AB, Fenn WO, Rahn H. Mechanics of breathing in man. J Appl Physiol 1950; 2: 592–607.

met with the inventor and expressed interest in learning more about the technology and marketing it. Yet, several years later in 1994, an article was published by a group of researchers, some of them employed at Hamilton Medical, which described the clinical evaluation results of a closed-loop system for mechanical ventilation called adaptive lung ventilation (ALV) [16]. In this system respiratory mechanics data were used to compute optimal rate and tidal volume of breathing in mechanical ventilation to minimize the work rate of breathing using the same procedure and formula that were described earlier in the patented invention [13]. Despite the fact that some of the authors of the article on ALV were quite familiar with the earlier invention also through previous meetings and discussions with the inventor, and that the fundamentals of the evaluated system in their article were the same as those described for an embodiment of the patent covering the invention, there was no reference to the patent or the publications linked to it in the article on ALV. After several years, Hamilton Medical marketed a technology for closed-loop control of ventilation called adaptive-support ventilation (ASV) which was a variation of ALV, and described by one of the more simple embodiments of US Patent 4986268 [13]. This mode was marketed under license of the patent by Hamilton Medical in later years as a result of a lawsuit that settled in 2004.

In early 1990s another patented closed-loop system for weaning from mechanical ventilation was

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16 Laubscher TP, Heinrichs W, Weiler N, Hartmann G, Brunner JX. An adaptive lung ventilation controller. IEEE Trans Bio-med Eng 1994; 41: 51–59.

introduced [17,18]. This was an intrabreath technique called proportional assist ventilation (PAV). Using this method, the ventilator measured the flow rate and the volume of gas inhaled by a spontaneously breathing patient on the machine and delivered pressure support that was proportional to the elastic and resistive components of pressure developed by the patient. This system was only suitable for patients with reasonably strong spontaneous breathing effort. More details of this technique will be described in the 2nd part of this article.

In late 1980s to early 1990s a number of automatic protocol driven systems for weaning from the ventilator were introduced. The first one of those systems used the measured pressure in the endotracheal tube of the patient as an indicator of the strength of spontaneous breathing and based on that measurement adjusted the length of mandatory breaths in the intermittent mandatory ventilation (IMV) mode [19]. The next protocol-driven system for weaning was introduced in 1991 [20]. This system used a laptop computer interfaced with a pulse oximeter that contin-

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17 Younes M, Lung ventilator device. US Patent No. 5,044,362, issued September 3, 1991.

18 Younes M. Proportional assist ventilation, a new approach to ventilatory support. Am Rev Respir Dis 1992; 145: 114–120.

19 Hernandez C, Moret V, Arcay B, Hermida RC. Weaning from mechanical ventilation using a prototype closed-loop system. Microcomput Appl 1988; 7(3): 128–130.

20 Strickland JH Jr, Hassan JH. A computer-controlled ventilator weaning system. Chest 1991; 100: 1096–1099.

uously measured the patient's arterial oxygen saturation. The computer checked the spontaneous breathing rate, minute ventilation, and oxygen level of the patient who was placed on the SIMV + PS mode periodically. If the measured values were acceptable, first the rate of mandatory breaths was incrementally reduced, and then the level of pressure support was gradually decreased until the patient was weaned. If any of the measured data fell outside an acceptable range, the computer increased the level of support.

This was followed by another protocol-driven system for weaning [21]. In this system, three indicators were used for weaning; the spontaneous breathing rate, tidal volume, and PetCO2. If these measurements were in the acceptable ranges, the level of support for the patient who was placed on the PS mode was decreased incrementally until he/she was ready for extubation. If any of the measured data fell outside the "comfort zone," the level of support by the machine was increased.

The next protocol-driven system for weaning was introduced in 1993 [22]. This was a slightly modified version of the system presented in 1991 by the same researchers [20]. This system was used in a similar manner to the earlier version except that it measured tidal volume instead of minute ventilation, and although arterial oxygen saturation of the patient was still monitored continuously by use of a pulse oximeter,

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21 Dojat M, Brochard L, Lemaire F, Harf A. A knowledge-based system for assisted ventilation of patients in intensive care units. Int J Clin Monit Comput 1992; 9: 239–250.

22 Strickland JH Jr, Hassan JH. A computer-controlled ventilator weaning system. Chest 1993; 103: 1220–1226.

but oxygen was no longer used as an indicator for weaning.

In mid to late 1990s two automatic systems for mechanical ventilation that used fuzzy logic control procedures were presented. The first one introduced in 1996[23] automatically controlled the rate and tidal volume of breathing based on measured values of PetCO2 during anesthesia. The second system presented in 1999 was a protocol driven technique for weaning patients on PS mode [24]. This system created fuzzy sets based on four inputs and the rates of changes of those inputs which were: heart rate, tidal volume, respiratory rate, and arterial oxygen saturation. The level of support provided by the ventilator was adjusted based on the measured indicators. This system was designed to wean patients suffering from chronic obstructive pulmonary disease (COPD) from the ventilator.

Another automatic system for mechanical ventilation was introduced in 1996 [25,26]. In this technique

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23 Schaublin J, Derighetti M, Feigenwinter P, Petersen-Felix S, Zbinden AM. Fuzzy logic control of mechanical ventilation during anaesthesia. Br J Anaesth 1996; 77: 636–641.

24 Nemoto T, Hatzakis G, Thorpe CW, Olivenstein R, Dial S, Bates JHT. Automatic control of pressure support mechanical ventilation using fuzzy logic. Am J Respir Crit Care Med 1999; 160: 550–556.

25 Iotti G, Braschi A, Galbusera C. P0.1, breathing pattern and pressure support ventilation. Intensive Care Med 1996; 22(10): 1131–1132.

26 Iotti GA, Braschi A. Closed-loop support of ventilatory workload: The P0.1 controller. Respir Care Clin N Am 2001; 7(3): 441–464.

the airway pressure measured 0.1 s after the onset of inspiration (P0.1), and the alveolar ventilation were used as indicators to increase or decrease the level of support in the PS mode. In this system, if P0.1 was lower than a preset value and alveolar ventilation was higher than a target level, level of pressure support was decreased. Otherwise, any other combination of alveolar ventilation and P0.1 dictated an increase in the pressure support level. Setting the target values for alveolar ventilation and P0.1 was a critical factor in successful application of this weaning technique. This system did not represent a classical continuous positive feedback control system and therefore was not inherently unstable due to the fact that the patient's airway pressure was only measured at a single distinct point during inspiration and chosen as an indicator for weaning. This system could not prevent hypoventilation and was subject to noise in the presence of disturbances such as coughing.

Another closed-loop method for control of ventilation that used an estimation of the patient's arterial CO2 tension as control variable was presented in 2002 [27]. This was a variation of the MMV technology [1] in which the level of minute ventilation was periodically calculated by the ventilator based on the patient's estimated CO2 level.

In parallel to many automatic systems for control of weaning and/or the amount of breathing gas supplied to the patient, many other automatic

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27 Fernando T, Cade J, Packer J. Automatic control of arterial carbon dioxide tension in mechanically ventilated patients. IEEE Trans Biomed Eng 2002; 6: 269–276.

systems for control of patient's oxygenation were developed in the last several decades.

A system for automatic adjustment of FIO2 for neonates suffering from respiratory distress syndrome (RDS) was introduced in 1979 [28]. An intra-arterial electrode and an oxygen analyzer were used to provide the input data to the system.

Another closed-loop technique for control of FIO2 in neonates was introduced in 1985 [29]. This system used the neonate's oxygen level measured by transcutaneous monitoring and adaptive control procedures to calculate the required level of FIO2. The next computer controlled system for improvement of oxygenation was designed to automatically adjust the level of PEEP [30]. Three algorithms were tested in the study and according to the reported findings; the one which was based on normalizing the fractional residual capacity (FRC) produced the optimal results in the shortest period of time.

A closed-loop technique for control of FIO2 that used arterial oxygen saturation as input was introduced in 1987 [31]. This system incorporated a

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28 Beddis IR, Collins P, Levy NM, Godfrey S, Silverman M. New technique for servo-control of arterial oxygen tension in preterm infants. Arch Dis Child 1979; 54: 278–280.

29 Sano A, Kikucki M. Adaptive control of arterial oxygen pressure of newborn infants under incubator oxygen treatments. Proc IEE 1985; 132(Pt. D., No. 5): 205–211.

30 East TD, Adriano KP, Pace NL. Computer-controlled optimization of positive end-expiratory pressure. Crit Care Med 1986; 14: 792–797.

31 Yu C, He WG, So JM, Roy R, Kaufman H, Newell JC.

proportional-integral (PI) technique and used adaptive control algorithms. Another closed-loop system for control of FIO2 in neonates was presented in 1988 [32]. This system used arterial oxygen measurements made by use of an intra-arterial electrode to adjust FIO2.

A microprocessor-based system for control of FIO2 which used inputs from a pulse oximeter in neonates was introduced in 1992 [33]. This was followed by another microprocessor controlled system for adjustment of FIO2 in adults that also used patient's arterial oxygen saturation as input and incorporated a PI controller [34]. The next system was designed to control the levels of FIO2 and PEEP in adults based on measurements of arterial oxygen partial pressure or arterial oxygen saturation. This system's algorithm was based on clinical guidelines [35]. Around the same time, a closed-loop technique for control of FIO2 in neonates that used arterial oxygen saturation

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Improvement in arterial oxygen control using multiple model adaptive control procedures. IEEE Trans Biomed Eng 1987; 34 (BME-8): 567–574.

32 Dugdale RE, Cameron RG, Lealman GT. Closed-loop control of the partial pressure of arterial oxygen in neonates. Clin Phys Physiol Meas 1988; 9(4): 291–305.

33 Morozoff PE, Evans RW. Closed loop control of SaO2 in the neonate. Biomed Instr Tech 1992; 26: 117–123.

34 Tehrani FT. A microcomputer oxygen control system for ventilatory therapy. Ann Biomed Eng 1992; 20(5): 547–558.

35 Anderson JR, East TD, Coombs J, Clemmer T, Orme J, Weaver L. Clinical trial of a non-linear closed-loop controller for oxygenation during ARDS. Crit Care Med 1994; 22: A188.

as input was presented [36]. A PID algorithm was used in the controller in this system.

Another closed-loop system for control of FIO2 in adults was introduced in 1997 [37]. This system used arterial oxygen saturation data as input and incorporated artifact rejection techniques. The computer algorithm used a PID procedure in this system.

The systems that have been developed more recently, tend to combine closed-loop techniques for delivery of optimal ventilation with automatic methods of controlling PEEP and/or FIO2 [38,39,40]. Some of these techniques are designed to control tidal volume, respiratory rate, inspiratory pressure, the inspiratory-to-expiratory time ratio (I:E), FIO2, and PEEP by using feedback closed-loop control techniques [39]. Another recent system [40], which is the subject of a new patent application, combines the features for

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36 Tehrani FT, Bazar AR. A feedback controller for supplemental oxygen treatment of newborn infants: a simulation study. Med Eng Phys 1994; 16: 329–333.

37 Raemer DB, Ji X-B, Topulos GP. FIX controller: An instrument to automatically adjust inspired oxygen fraction using feedback control from a pulse oximeter. J Clin Monit 1997; 13: 91–101.

38 Tehrani F, Rogers M, Lo T, Malinowski T, Afuwape S, Lum M, Grundl B, Terry M. A dual closed loop control system for mechanical ventilation. J Clin Monit Comput 2004; 18: 111–129.

39 Tehrani FT. Method and apparatus for controlling a ventilator. UK Patent Serial No. GB2423721, Granted 14 October, 2008. (Patent pending in several other countries).

40 Tehrani FT, Roum JH. FLEX: A new computerized system for mechanical Ventilation. J Clin Monit Comput 2008; 22: 121–130.

closed-loop control of ventilation with new features for control of more ventilatory variables such as PEEP and FIO2, as well as control of weaning in adults, pediatrics, and neonatal patient populations. All these systems [38–40] include the features of a ventilation technique known as adaptive support ventilation (ASV) which was originally introduced in 1991 [13], and augment those by many added closed-loop techniques for control of other ventilatory parameters.

Table 1 shows the categories of automatic systems for control of mechanical ventilation. It shows systems that are based on closed-loop techniques from an engineering standpoint, as well as those that are protocol-driven. The technologies categorized in this table include those designed to control ventilation, weaning, and oxygenation, either individually or in combination.

Table 1. Various categories of automatic systems for mechanical ventilation

Automatic closed-loop systems
Ventilation controllers [4–14, 23, 25–27]
Weaning controllers [17, 18]
FIO2 and/or PEEP controllers [28–34, 36–39]
Ventilation + (PEEP and/or FIO2) controllers [38, 39]
Ventilation + PEEP + FIO2 + weaning controllers [40]
Automatic protocol-driven systems
Ventilation/weaning controllers [19–22, 24]

FIO2 and/or PEEP controllers [35]

Systems are identified by their cited reference numbers and are separated by commas.

Discussion and Conclusion

Many automatic systems for control of the main outputs of mechanical ventilators in the management and/or weaning phases of treatment have been developed by researchers in the field. In closed-loop control techniques, it is important not to base the technique on a single control variable such as arterial PCO2 or PetCO2. Systems that use only one variable to control ventilation may mask respiratory problems and cause provision of inappropriate treatments. The automatic systems whether protocol-driven or closed-loop feedback controlled, need to have effective methods of artifact rejection in place to avoid propagation of errors. Furthermore, in closed-loop feedback controlled systems in particular, data abstraction and smoothing techniques may need to be incorporated to prevent abrupt and/or inappropriate treatments offered.

Closed-loop systems designed to control FIO2 with or without automatic titration of PEEP, need to be sufficiently robust to tackle abrupt disturbances in oxygen balance of the patient. The systems that are based on fine control algorithms such PI or PID techniques alone, will likely need to be enhanced to gain higher speed and efficiency in correcting and preventing hypoxia if the patient's oxygen level falls abruptly. Automatic systems that can be used in different phases of treatment and can control a wider range of ventilator's outputs are likely to be of more use to clinicians than more restricted systems in future.

Also, neuro-fuzzy techniques may need to be further explored in control of different aspects of mechanical ventilation.

The 2nd part of this article will focus on the analysis of automatic systems that have been commercialized, and a discussion of the likely trends in the technology of mechanical ventilation in the years to come.

LAURENCE C. CARMICHAEL ET AL.,
***DIAGNOSIS AND THERAPY OF ACUTE RESPIRATORY DISTRESS SYNDROME IN ADULTS: AN INTERNATIONAL SURVEY*,**
11 J. CRITICAL CARE 9 (MARCH 1996)

JOURNAL OF CRITICAL CARE, VOL. 11 (MARCH 1996)

Diagnosis and Therapy of Acute Respiratory Distress Syndrome in Adults: An International Survey

Laurence C. Carmichael, Paul M. Dorinsky, Stanley B. Higgins, Gordon R. Bernard, William D. Dupont, Bridget Swindell, and Arthur P. Wheeler

Journal of Critical Care, Vol. 11 (March 1996): pp 9-18

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In an attempt to identify the range of opinions influencing the diagnosis and therapy of patients with the adult respiratory distress syndrome (ARDS), a postal survey was mailed to 3,164 physician members of the American Thoracic Society Critical Care Assembly. The questionnaire asked opinions regarding the factors important in the diagnosis of ARDS and its treatment. Thirty-one percent of physicians surveyed responded within 4 weeks, the vast majority of which were board certified or eligible in Internal Medicine, Pulmonary Disease, and/or Critical Care Medicine. A known predisposing cause, measure of oxygenation efficiency, and a chest radiograph depicting pulmonary edema were reported to be the most important criteria for a clinical and research diagnosis of ARDS. Lung compliance and bronchoalveolar lavage neutrophil or protein content were reportedly less important. The initial treatment of patients with ARDS was reported to be most commonly accomplished using volume-cycled ventilation in the assist/ control mode. Nearly half the responders reported using lower tidal volumes (5 to 9 mL / kg) than the traditionally recommended 10 to 15 mL/ kg. Most respondents indicated they have intentionally allowed CO2 retention. On average, oxygen toxicity was thought to begin at an FI02 between 0.5 and 0.6. It was reported that modest levels of positive end-expiratory pressure (PEEP) were used in incremental fashion as FiO2 requirements increased. Perceived indications for insertion of pulmonary artery catheters and compensation of the effects of PEEP on the pulmonary artery occlusion pressure varied widely among the responders. We conclude that reported practice patterns regarding the care of ARDS patients vary widely even within a relatively homogenous group of critical care practitioners.

IT HAS BEEN nearly 25 years since Ashbaugh et al[1] described the syndrome of acute respiratory distress in adults and introduced the term, ARDS. The syndrome was originally described in patients with dyspnea, tachypnea, cyanosis refractory to oxygen administration, loss of lung compliance, and diffuse alveolar infiltrates caused by a wide spectrum of precipitating factors. In the original report, positive end-expiratory pressure (PEEP) was the most beneficial therapeutic modality.[1] Although the ability to support the lung and other failing organs has improved in the past 25 years, little in the way of specific therapy exists. As a result, new ideas and therapeutic modalities are constantly surfacing and being proposed as potentially efficacious in the management of ARDS. Despite these advances, mechanical ventilation remains the mainstay of patient support during acute respiratory failure. There is increasing evidence that mechanical ventilation itself may cause microenvironmental pulmonary damage via oxygen toxicity as well as pressure and volume stresses. Recent reports acknowledge the need to develop a consensus approach to the practice of mechanical ventilation in respiratory failure. However, to our knowledge, the practice patterns of physicians engaged in treating patients with ARDS have yet to be defined or at least queried. Given the widespread availability of information on the treatment of ARDS, we hypothesized that the diagnostic and therapeutic approach to ARDS would vary little among physicians trained in critical care. To test this hypothesis, and describe the self-reported views and practices of a group of critical care physicians, we conducted a direct mail survey of the diagnostic and therapeutic

practices of members of the Critical Care Assembly of the American Thoracic Society.

Materials and Methods

A questionnaire was designed to survey the beliefs of critical care practitioners regarding the diagnosis and therapy of ARDS. A pilot questionnaire was administered to 10 physicians in the pulmonary-critical care section of one academic medical center. After suggested revisions, the survey was administered to a second group of practicing pulmonary-critical care physicians for additional comment. The resulting final survey tool was able to be completed in less than 20 minutes. After final revision, an anonymous single mailing of the questionnaire to all 3,264 members of the American Thoracic Society Assembly of Critical Care Medicine was conducted in late 1992. An accompanying cover letter encouraged physicians to respond and assured participants anonymity. Financial limitations prevented repeated mailings to nonresponders or fiduciary incentives to boost response rates.[29] Data collection was limited to a 4-week period to provide a discrete snapshot of reported attitudes at the time of the survey.

A variety of question types were used, including commonly used analog ranking scales to relative strength of opinion regarding diagnostic criteria.[3,6] Binary questions were used to determine if a given opinion or practice was ever held or used. Categorical questions such as those related to preferred mode of ventilation and tidal volume and open-ended questions designed to elicit the bounds of reported practice were also included.

In addition to obtaining basic demographic information, the survey sought to determine how practicing physicians diagnose and treat ARDS. Physicians were asked to rank the importance of criteria on which a clinical and research definition of ARDS should be based. An analog linear scale was used to allow responses to be expressed as a continuous variable. Respondents were asked questions with categorical answers about modes of mechanical ventilation used and tidal volume size. In addition, dichotomous questions were asked to determine whether modes and volumes were selected and altered based on airway pressures. Categorical questions were included to help determine how and why practitioners use monitoring devices (e.g, pulmonary artery catheters), how they used PEEP, and how (if) they corrected the wedge pressure for the effects of applied PEEP. Lastly, we determined how physicians apply PEEP at various levels of arterial oxygenation and what "best PEEP" actually represents.

Data from the questionnaires returned within 4 weeks were entered into a database, PARADOX (Borland Software, Scotts Valley, CA). Summary calculations and descriptive statistics were performed using Number Cruncher Statistical System (NCSS; Dr Jerry L. Hintze, Kaysville, VT) and reported as the mean ± standard error unless otherwise noted. A copy of the questionnaire is reproduced in the Appendix.

RESULTS

Characteristics of Respondents

Within 4 weeks of distribution, 1,023 of 3,264 (31.1%) questionnaires were completed and returned.

Responses were received from all 50 of the United States and 24 countries other than the United States. The proportion of responders by geographic region paralleled that of the overall enrollment of the group surveyed. The mean age of responders was 42 ± 7 years and nearly all (90%) were between 30 and 55 years of age. Equal numbers practiced in university teaching (43%) and community hospitals (42%). Similarly, combined medical-surgical and strictly medical ICUs made up 52% and 37% of the practice settings, respectively.

The majority (65%) of physicians were board certified internists and certified in pulmonary and/or critical care medicine. Eighty percent were board eligible or certified. The small numbers of assembly members who describe themselves as pediatricians, surgeons, or anesthesiologists precluded meaningful group comparisons by medial specialty. No differences existed in answers to specific questions when responders were stratified by age, board certification status, hospital type or size, or type of intensive care unit practice. Physicians who were board certified in critical care medicine spent a higher percentage of their time practicing critical care (42% ± 25%) than those not board eligible or certified (26% ± 22%, $P = .05$). Respondents reported spending an average of 64% of their time engaged in clinical activities, 14% in research, and 12% in teaching.

The Definition of ARDS

Surveyed physicians were asked to mark on a 115 mm analog scale from "unimportant" to "very important" the perceived relative importance of six factors (i.e., predisposing condition, oxygenation, lung compliance,

radiographic abnormality, measurement of left ventricular filling pressure, and results of bronchoalveolar lavage) in making the diagnosis of ARDS for clinical and research purposes. The position of the mark was measured then converted to a numerical value between 1 (unimportant) and 115 mm (very important). The mean, standard deviation, and 10th, 25th, 75th, and 90th percentiles are reported each response (Fig 1).

The majority (74%) indicated that a known clinical predisposing cause, a measure of oxygen transfer efficiency (93%), and a chest radiograph depicting pulmonary edema (93%) were at least moderately important in making a clinical diagnosis of ARDS. Only half considered lung compliance important, although nearly

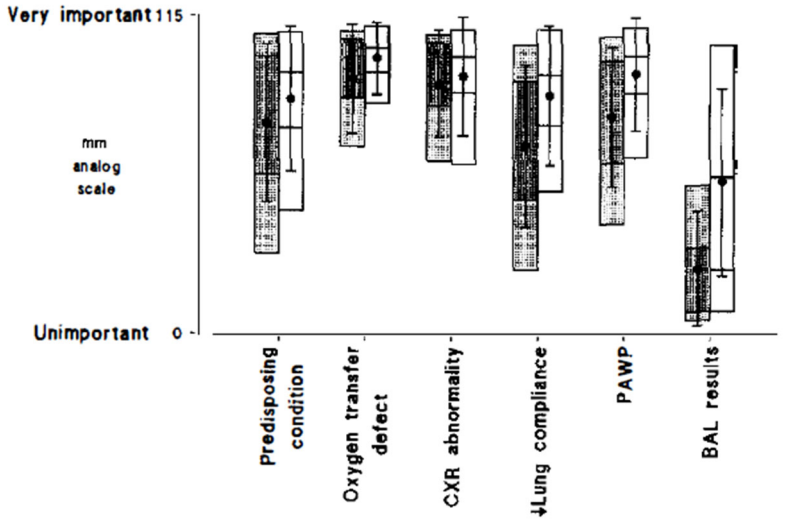

Fig 1. The relative importance of six factors considered important for a clinical and research definition of ARDS (☒ clinical; ☐ research; data displayed as mean,

10th, 25th, 75th, and 90th percentile ± standard deviation).

all stated that bronchoalveolar polymorpho-nuclear leukocyte count or protein content were unimportant for a clinical diagnosis. Finally, each defining factor held greater importance in the research setting (Fig 1).

Therapy of ARDS

Ventilation

Assist/control was by far stated to be the favored ventilatory mode (Fig 2), although the group was almost evenly split between an initial tidal volume selection of 5 to 9 mL/kg (45%) and 10 to 13 mL/kg (48%; Fig 3). Nearly all (96%) stated that the level of airway pressure influenced their choice of tidal volume. More than 97% of all respondents stated they did not insert chest tubes on a prophylactic basis to treat anticipated barotrauma. Interestingly, 79% indicated that they intentionally allow carbon dioxide retention in mechanically ventilated

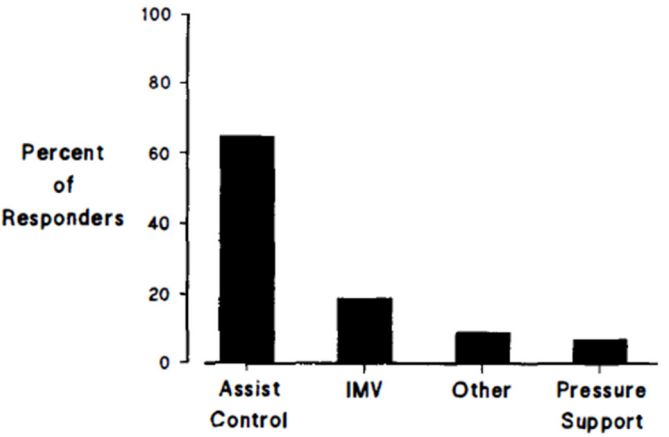

Fig 2. The favored modes of mechanical ventilation in ARDS.

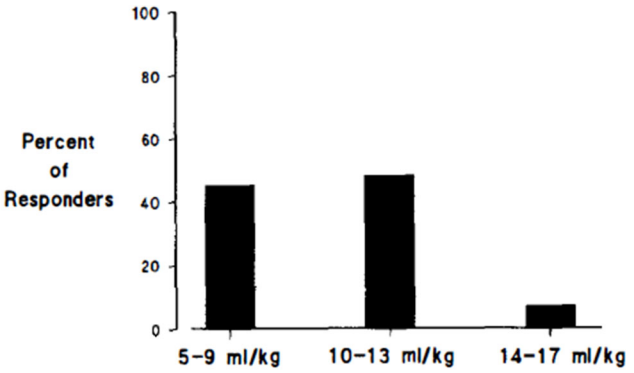

Fig 3. The most often selected tidal volume for mechanical ventilation in ARDS.

ARDS patients, although no data were collected regarding the frequency that this practice is used or the extent to which hypercarbia was allowed.

Oxygenation / Oxygen Toxicity

Sixty-two percent of respondents indicated that the lowest acceptable long-term arterial oxygen saturation was 86% to 90%, whereas saturations of 91 % to 95% were the lowest considered acceptable by another 21 % of responders. Almost all (94%) reported they had used an FIO2 exceeding 0.60 for more than 48 hours, even though 44% of respondents indicated that FIO2s greater than 0.60 have some degree of toxicity. The collective opinion of the level of FIO2 at which oxygen toxicity begins is shown in Fig 4. Respondents indicate that FIO2s between 0.50 to 0.60 were the most common minimally toxic concentration if used longer than 48 hours. Nonetheless, unsolicited,

a large number of respondents indicated uncertainty concerning the levels at which oxygen toxicity begins.

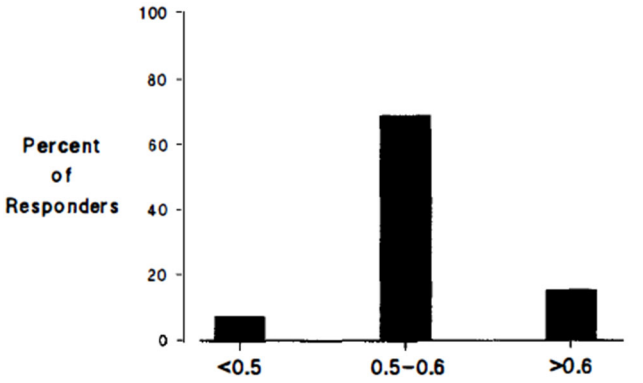

Fig 4. Toxic oxygen concentrations used for 48 hours or more.

Use of PEEP

Although the terms "prophylactic" or "physiologic PEEP" were not explicitly defined in the questionnaire, 13% said they used "prophylactic PEEP" and 54% replied that they used "physiologic PEEP." A number of those questioned did not indicate a perceived level of "best PEEP" in the typical patient; however, 60% of those answering indicated that the "typical best PEEP" is between 6 and 10 cmH2O and 36% indicated that it is between 11 and 15 cmH2O. The average value believed to be the "typical best PEEP" was 11 ± 5 cmH2O. There were a number of methods reportedly used to determine best PEEP, and the most common are shown in Fig 5.

When physicians were asked to report the highest PEEP level they had ever used, responses ranged from 2 to 100 cmH2O, with a mean response

of 24 ± 7 cmH2O. Ninety percent of those surveyed had not used a level of PEEP greater than 30 cmH2O. When asked what PEEP value they would not exceed, most indicated that there was no absolute limit of PEEP they would not exceed. Among those advocating a specific level of PEEP they would not exceed, the response was 24 ± 8 cm H2O (close to the value given for the maximum PEEP they had used in the past).

Finally, because applied PEEP may alter measured wedge pressure, we asked physicians how they compensated for this effect (Fig 6). Subtraction of some fraction of applied PEEP from measured wedge pressure and no attempt at compensation were the most common responses, occurring with nearly equal frequency.

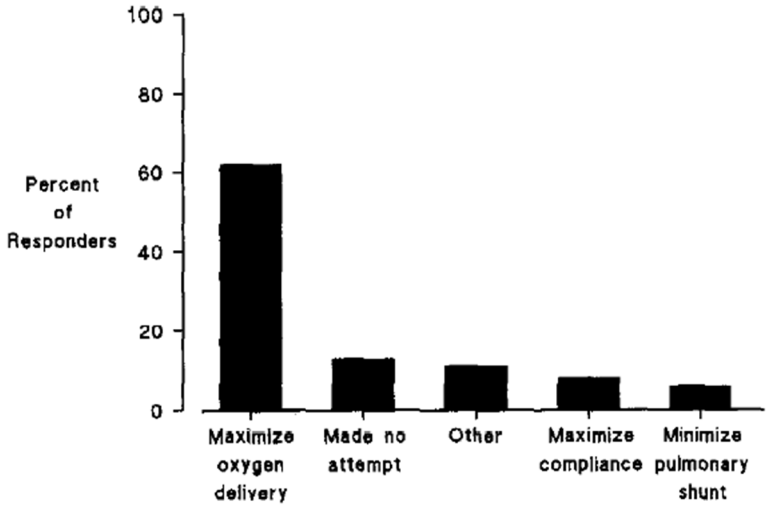

Fig 5. The favored methods of determining "best PEEP."

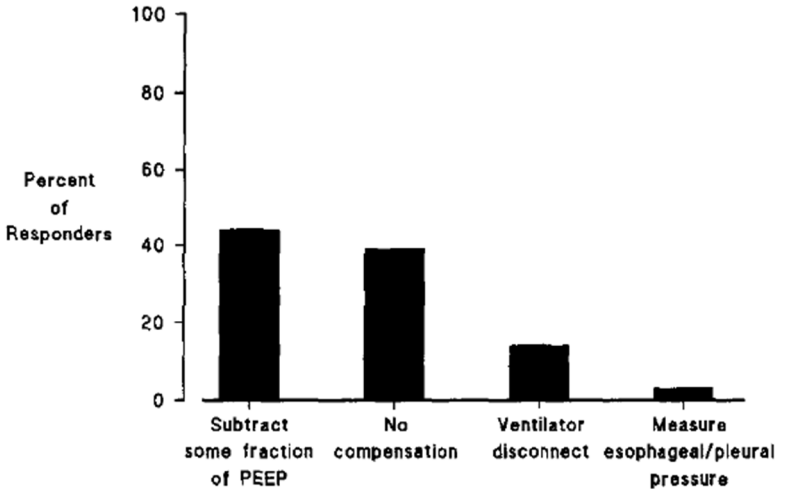

Fig 6. The methods of compensating pulmonary capillary wedge pressure for PEEP effects.

PEEP and Inspired O2 Levels

At a range of FIO2s from 0.21 to 1.0, physicians were asked to choose a level of PEEP that would not be exceeded before increasing to the next higher FIO2. At an FIO2 of 0.5, the mean maximum PEEP applied was 11 cm H2O, 16 ± 6 cmH2O at 0.6, 20 ± 6 cmH2O at 0.8, and 23 ± 7 cmH2O at 1.0 (Fig 7).

The Use of Pulmonary Artery Catheters

The indications for the insertion of pulmonary artery catheters in the management of patients with ARDS are shown in Fig 8. Although hypotension was the single most commonly reported reason for pulmonary artery catheter insertion, routine placement was indicated by approximately one-third of responders.

When asked to provide an optimal pulmonary capillary wedge pressure (PCWP), 48% indicated a

desire to maintain PCWP of 11 to 15 mmHg, whereas another 50% indicated that 6 to 10 mmHg was optimal. Few respondents indicated that they attempted to maintain PCWPs less than 5 or greater than 15 mmHg.

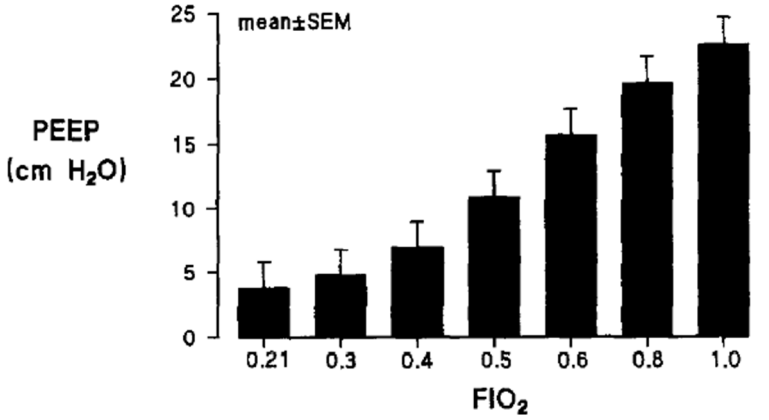

Fig 7. The maximum PEEP used at various FIO2s.

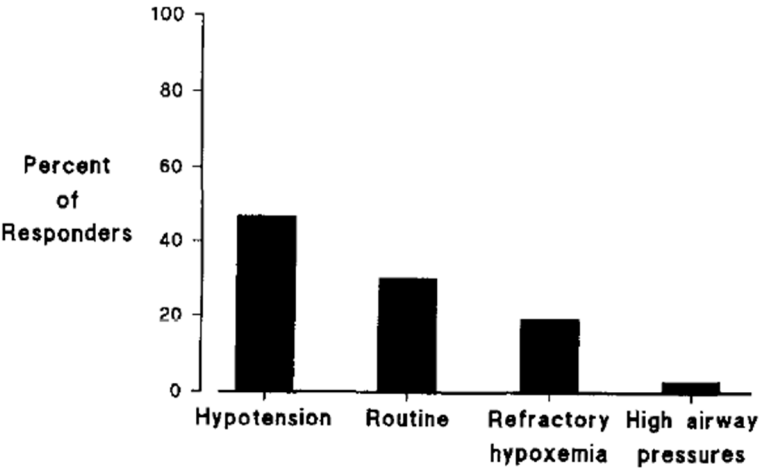

Fig 8. Indications for the use of pulmonary artery catheters.

DISCUSSION

Since the mid 1960s, when mechanical ventilation began to be used for long-term patient support, ARDS has continued to challenge intensivists in terms of the clinical situation in which it is encountered, its diagnosis, and its treatment. Despite major advances in critical care medicine, specific causes and therapeutic agents for ARDS have been elusive. As experience mounts in supporting patients with acute respiratory failure both in the research and clinical setting, it has become increasingly clear that mechanical ventilation can be both life-preserving as well as potentially harmful. These facts have been borne out in several recent communications urging physicians to reassess their outcome objectives of ventilatory support,[18] whereas others suggest the need to build a consensus view on the use of mechanical ventilation in patients with acute lung injury.[17]

We prepared this questionnaire to attempt to determine how ARDS is being defined and mechanical ventilation is being used by a relatively homogeneous group of critical care practitioners and thus targeted the ATS Critical Care Assembly. This survey was not intended to be a comprehensive random sample of physicians practicing critical care medicine. This group is composed primarily of physicians whose postgraduate medical training was in internal medicine, further subspecializing in pulmonary medicine, and who have additional qualifications or certification in critical care medicine (80% board eligible/certified in both pulmonary and critical care medicine). The equal distribution between community practice and that in university teaching hospitals and the overall 64% time commitment to clinical practice suggests we

sampled practicing physicians. In fact, Critical Care Assembly members spent a greater proportion of their time in clinical activities than the average ATS member (data not shown). There are only a relatively small number of surgeons, anesthesiologists, and pediatricians in this assembly and it is recognized that their attitudes and reported practice may differ; hence, no conclusions regarding their activities can be drawn from this study.

Although these data do not represent the entire ATS critical care assembly and should not be interpreted as an official position of the society, the overall 31% response rate was unexpectedly high from a single mailing without further reminders or incentive. This response rate was similar to other recent large postal surveys regarding critical care issues.[8,16]

In past reports, the definition of ARDS often included a severe reduction in PaO2/FIO2 ratio (< 200 and, in some cases, < 150 mmHg), diffuse radiographic infiltrates, reduced lung compliance, and normal left ventricular filling pressures occurring in a compatible clinical setting.[1,20,22,23] Today, practitioners use similar criteria, namely, abnormal gas exchange, diffuse radiographic infiltrates, and a normal pulmonary artery wedge pressure. Abnormal lung compliance and the clinical setting are not considered as important in clinical decision making and bronchoalveolar lavage (despite being a major research tool) does not appear important in defining ARDS clinically.

Conventional teaching in the 1970s suggested that ventilation in ARDS patients be supported by a volume cycled ventilator using assist-control or intermittent-mandatory mode and using tidal volumes of 10 to 15 mL/kg with or without sigh breaths. At that

time it was commonly recommended that ventilation be directed toward maintaining a normal systemic pCO2 and pH.24 Reduction of the peak inspiratory pressure at the cost of decreased alveolar ventilation (hypercarbia) or decreased arterial oxygen saturation was not advocated. Bedside oximetry and oximetric pulmonary artery catheters were not widely available. Likewise, many references indicated that a PaO2 > 60 mmHg was desirable and should be achieved through the use of increased FIO2s and incremental application of PEEP.28 More recently, these goals of mechanical ventilation in ARDS have been challenged. In the early 1990s it was recognized that high peak inspiratory pressures could induce lung injury and pressure-limited, low tidal volume, synchronized intermittent mandatory ventilation with permissive hypercapnia was reported.[14] An impressive survival rate of 84% further stimulated interest in limiting peak inspiratory pressure and tidal volume and allowing the pCO2 to increase.[13]

The initial reported choice of ventilatory modes is still assist/control at lower tidal volumes than previously recommended (i.e, < 10 mg/kg) and the practice of permissive hypercapnia is extremely common. We speculate that these actions represent strategies to limit airway pressure and subsequent barotrauma. In addition, albeit the assist/control mode was still the preferred ventilatory mode, intermittent mandatory ventilation with or without pressure support was favored by a substantial minority. Pressure limited modes of ventilation appear to be used infrequently despite the relatively high profile these modes have had in recent reports.[19]

Practices involving hemoglobin-oxygen saturation and avoiding toxicity may have changed over the years for uncertain reasons. In particular, many respondents accept oxygen saturations of 86% to 90%, a level of hemoglobin-oxygen saturation that is lower than the level traditionally recommended (SaO2 of 90%). The lower range of saturations accepted (although not necessarily desired) is not based on available scientific data. In fact, a number of studies have concluded that oxygen delivery and consumption are lower in nonsurvivors of ARDS and that consumption may rely on delivery in some patients with ARDS.[25,26] Therefore, strategies that result in decreased hemoglobin-oxygen saturation and cardiac output remain controversial.

Concerning oxygen toxicity, most respondents believe that little oxygen toxicity occurs before the FIO2 exceeds 0.50 to 0.60. This may reflect the opinion largely based in animal experiments that the injured (inflamed) lung is more resistant to the toxic effects of oxygen than are normal lungs.[4,7] However, numerous respondents spontaneously commented that there was no reliable human data on which to base these conclusions.

To examine the patterns of PEEP and oxygen use, we asked respondents to indicate the maximum PEEP that would be used at any given FIO2 before increasing the FIO2. It was uncommon for respondents to use more than 10 cm H2O PEEP until nearly toxic range oxygen concentrations were reached (0.50 to 0.60). Even in the scenario in which patients were receiving 100% oxygen, the average maximum applied PEEP did not exceed 25 cmH2O. Although there was no universal method of determining "best PEEP,"

there was a remarkably consistency regarding what "best PEEP" turns out to be. Seventy-two percent of respondents indicated that, regardless of the method used to determine PEEP, levels between 10 and 15 cmH2O typically turn out to be the "best PEEP." To many, the "best PEEP" is the least PEEP at which hemoglobin-oxygen saturation is considered adequate on nontoxic concentrations of inspired oxygen.33 We speculate the incremental conservative application of applied PEEP suggests a greater concern or uncertainty regarding the complications of airway pressure than for oxygen toxicity. The use of high levels of PEEP reported in the literature, so-called "super PEEP," was not reflected in this survey.[15,33]

There are countless citations outlining the usefulness of pulmonary artery catheters in patients with ARDS. Touted benefits have included establishment of the diagnosis of noncardiogenic pulmonary edema and optimization of the cardiac output while adjusting the PEEP and FIO2. [5,9,10,27,30,31] This group of surveyed physicians displayed considerable disagreement regarding the use and interpretation of pulmonary artery catheters and the data they provide. The most common indication for their insertion was "routine." Although applied PEEP may not affect the measured airway pressure or the PCWP at levels < 15 cm H2O,[21] most respondents subtracted some fraction of the applied PEEP from the PCWP measurement while few opted for the most direct compensation, esophageal/pleural pressure measurement. Finally, almost 20% of physicians said they use ventilator disconnection, a technique some have described as unsafe.[32]

Data contained herein are subject to many limitations and should not by themselves be used to change or justify a particular belief or practice. These data should not be used to classify a particular practice as good or bad. The major limitation of this type of survey is nonresponder bias. That is, the opinions and practices of those who chose not to respond are unknown and may differ substantially from responders. We can only speculate on the beliefs of nonresponders. For example, nonresponders may have more unusual beliefs that they did not wish to acknowledge, even though this was an anonymous survey. Conversely, it is possible that the respondents have less conventional beliefs or practice styles and felt a desire to espouse their beliefs publicly. Nonresponder bias has been reported with response rates up to 60% to 70% in prior studies. However, the importance of this feared bias has been questioned. 2,11,12 A second potential source for bias is the homogeneity of the surveyed population that prevents comparison to other types of respondents. Finally, postal surveys such as this do not document current practice, but rather only the respondents' beliefs about their practice. Self-reported behavior studies are limited by this factor and require follow-up with observational clinical studies to document activities.

The results of this survey suggest that the approach to the diagnosis and therapy of ARDS may vary widely among a homogeneous group of critical care practitioners. Opinions were more consistent with regard to the diagnosis of ARDS, the mode of ventilatory support, and the use of PEEP. Also, these data suggest that certain treatment practices that are new, unproven, and potentially harmful are being

used by a substantial number of practitioners. Albeit the degree to which the results of this study may be generalized is limited, it does indicate considerable degrees of variation among these practitioners and may, in part, account for at least some of the difficulties in conducting and interpreting the results of large, multicenter, clinical trials. This study is not intended to define practice patterns, but rather suggest areas of further study and consideration.

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A Closed-Loop Controller for Mechanical Ventilation of Patients with ARDS

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KEYWORDS

Closed-loop control, Adult Respiratory Distress Syndrome, Mechanical Ventilation

ABSTRACT

Mechanical ventilators are routinely used to care for patients who cannot adequately breath on their own. Management of mechanical ventilation often involves a careful watch of the patient's arterial blood-oxygen tension and requires frequent adjustment of ventilation parameters to optimize the therapy. This situation lends itself as a candidate for closed-loop control.

This report describes a closed-loop control system based on well-established protocols to systematically maintain appropriate levels of positive end-expiratory pressure (PEEP) and inspired oxygen (FiO2) in patients with Adult Respiratory Distress Syndrome (ARDS). The closed-loop control system consists of an in-dwelling arterial oxygenation (PaO2) sensor (Pfizer Continucath), coupled to a Macintosh computer that continuously controls FiO2 and PEEP settings on a Hamilton Amadeus ventilator. The implemented protocols provide continuous closed-loop control of oxygenation and a balance between patient need and minimal therapy.

The controller is based on a traditional proportional-integral-derivative (PID) approach. The idea is to control, or maintain, the patient's PaO2 level at a target value determined, or set, by the patient's physician. The controller also features non-linear and adaptive characteristics that allow the system to respond more aggressively to "threatening" levels of PaO2. Another benefit of the control system is the ability to display, monitor, record and store all system parameters, settings, and control variables for future analysis and study.

The system was extensively tested in the laboratory and in animal trials prior to use on human subjects. The results of a small clinical trial indicated that the system maintained control of the patient's therapy nearly 84% of the time. During the remainder of this time, the controller was interrupted primarily for suctioning, PaO2 sensor calibration or replacement. The response of the closed-loop controller was found to be appropriate, reliable and safe in patients with ARDS.

INTRODUCTION

Mechanical ventilators are used to care for patients that experience respiratory abnormalities where proper treatment for the patient requires frequent adjustment of ventilation parameters for optimum therapy. Often a sample of the patient's blood is drawn and tested in the lab to determine the oxygen content. This sample interval is typically 4 to 8 hours. Based on the results of the blood test, the patient's physician modifies the therapy by directing adjustments to the mechanical ventilator. The problem is that the therapy is based on widely separated sample intervals and ventilator adjustments that cannot respond to short-term patient changes. This situation can be remedied by continuously monitoring the patient's blood oxygenation and responding with appropriate adjustments in a close-loop environment Although there are numerous closed-loop systems in most mechanical ventilators to optimize the machines performance, there are no closed-loop control systems to optimize FiO2 and PEEP delivery based on the patient's need. Almost all patients with fully developed ARDS require prolonged artificial respiratory support due to increases in lung stiffness

and gas exchange abnormalities, but when high concentrations of inspired oxygen or high airway pressures become necessary in a very ill patient, the ventilator itself may further damage the patient's lungs [1]. We have designed a system based on well-established protocols [2] for management of mechanical ventilation that provides continuous closed loop control of oxygenation and a balance between patient need and minimal therapy. A small clinical trial of this controller has been conducted at LDS Hospital in Salt Lake City, UT to demonstrate safety and effectiveness in patients with ARDS. Hopefully this careful management of potentially toxic therapies will improve outcome of patients with hypoxic respiratory failure.

METHODS

The closed-loop control system [3] for the management of arterial oxygenation consists of an indwelling PaO2 sensor coupled to a Macintosh computer that continuously controls FiO2 and PEEP on a Hamilton Amadeus ventilator as illustrated in Figure 1. The PaO2 is continuously measured by a Pfizer Continucath 1000 intra-arterial PaO2 monitor (Pfizer Inc., New York, NY). This requires the placement of a small PaO2 electrode in the patient's artery. An Apple Macintosh computer (Apple Computer Inc., Cupertino, CA) constantly reads the patient's PaO2 signal from the Continucath monitor, and computes appropriate values of PEEP and F1O2. These values are then sent to the Hamilton Amadeus (Bonaduz, Switzerland) mechanical ventilator, which then *delivers the* appropriate oxygenation therapy to the patient.

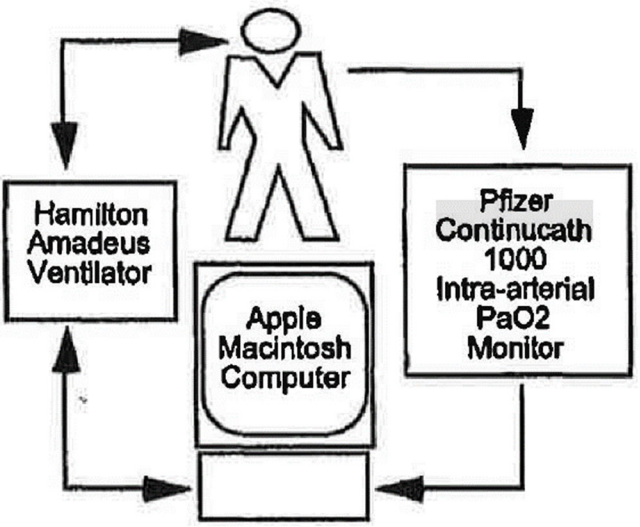

Figure 1. Hardware components of closed-loop control system.

The computer constantly reads important information from both the PaO2 monitor and ventilator via RS232 serial *ports*. This information is used to calculate new values of PEEP and FiO2 that are subsequently transmitted to the ventilator for proper adjustments in patient therapy.

We used National Instrument's Lab VIEW (6504 Bridge Point Parkway, Austin, Texas 78730-5039) to implement the closed-loop controller and create a user-friendly interface. LabVIEW is a graphical programming platform used primarily for data acquisition and instrument control with libraries containing many graphical controls and indicators, such as switches, knobs, dials, lights, graphs and strip charts. These controls and indicators make the user interface appealing and easy to use. For example, the main information screen makes use of color, pictures, and large numeric font to display the current values for PaO2,

PEEP, and FiO2. A strip chart displays the previous 6 hours of PEEP, FiO2 and PaO2 data. Virtual switches on this screen allow the user to easily change operation and data collection modes. A variety of warning indicators alert the user of potential problems.

The controller is based on a traditional proportional, integral and differential adaptive controller. The basic elements of the closed-loop controller are depicted in figure 2. These elements include: the look up tables or the decision mechanism, the FiO2 and PEEP PID controllers that calculate the amount of therapy adjustment, and the adaptive overall gain term. Also the patient's current PaO2 level and the target PaO2 level are included.

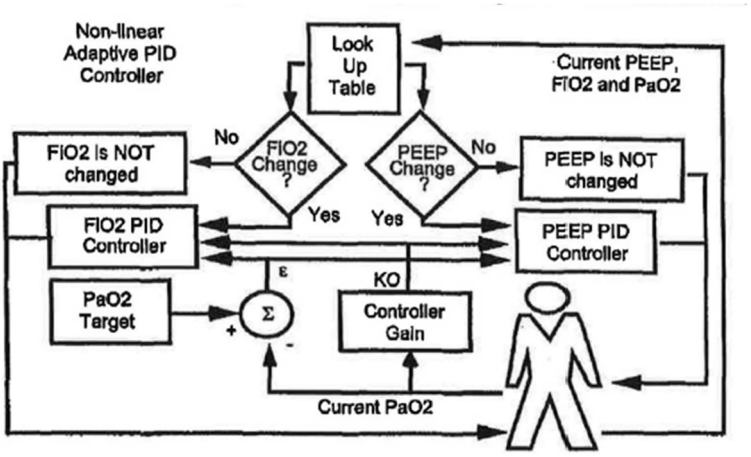

Figure 2. Components of the non-linear adaptive PID controller.

The look up tables, shown in figure 3, contain the logic used to dictate changes in therapy based on the patient's current level of PaO2 and the current PEEP and FiO2 settings. The five logic tables correspond to different levels of patient blood oxygenation where

patient's physician can. define the thresholds for each category. The decision-making logic in the tables have been extensively used and tested at LDS Hospital, in Salt Lake City, Utah.

The following equations describe the discrete recursive form of the PID controller used to calculate the appropriate change in oxygenation therapy.

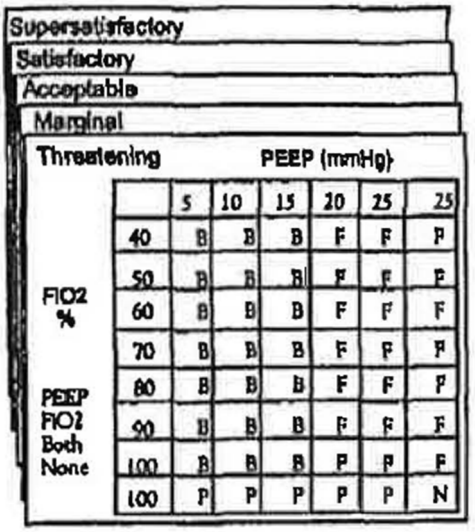

Figure 3. Look Up Tables determine the therapy parameters to be changed based on current PEEP, Fi02 and PaO2 category.

PEEP = PEEP + KO(E p0-E1 p1+ E2 p2) (eq. #1)

FiO2 = FiO2 + KO(E f0-E1 f1+ E2 f2) (eq. #2)

The error term E is the difference between the patient's current PaO2 value and the set point or target chosen by the patient's physician. The terms E1 and E2 are the previous two error values respectively. The constants associated with each error term provide appropriate proportional, integral and differential

gain. In cases of "threatening" low PaO2 values, the calculated change in FiO2 is increased for a more aggressive response.

The overall gain term, K0, is a function of the PaO2 saturation, and is adaptive in that the value of gain varies. A plot of the overall gain is shown in figure 4, which shows a more aggressive response to hypoxemia and a more conservative response to PaO2 above the desired goal. This provides a good balance between aggressive responses to "threatening" levels of PaO2 and slow reduction of therapy for levels of PaO2 greater than the target level.

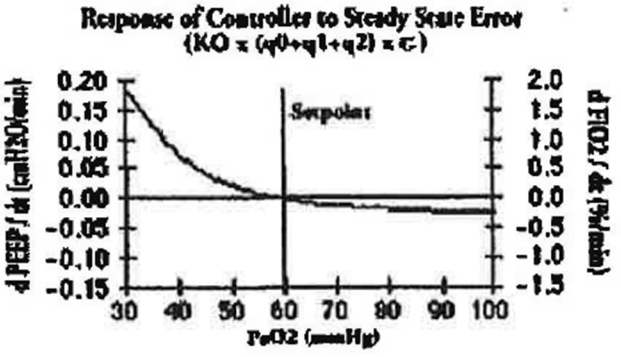

Figure 4. Adaptive gain adjusts rate of change for PEEP and FiO2 based on PaO2.

The safe operation of the system depends, in part, on reliable communication between devices. The Continucath data is constantly checked for errors or disruption by comparing current readings of PaO2 with past values. If erroneous readings are detected, a warning is displayed and the erroneous values are not used in the controller. The Hamilton Amedeus ventilator is designed to use manual control settings in the event that proper data communication is lost.

The computer warns the user, when necessary, to manually adjust the PEEP and FiO2 knobs on the Hamilton ventilator to current controlled values as a precaution to minimizes an abrupt change in therapy in the event of power failure or communication breakdown between the computer and the ventilator.

The closed-loop system was thoroughly tested under set conditions in the lab and realistic animal trials before clinical trials were performed.

The bench tests included a long-term recovery, or weaning, simulation with a "supersatisfactory" or high level of patient PaO2, and a rapid response simulation to critical or "threatening" low levels of PaO2. The system was also tested for cases of PaO2 sensor failure, computer power failure, and communication interruption or failure.

Previous versions of the controller were tested in five mongrel dogs with an oleic acid lung injury to simulate conditions of ARDS patients. After injury, the controller was activated and the animals' PaO2 and resulting computer controlled oxygenation therapy were monitored. We were also able to test the system's performance during routine interruptions such as nebulizing treatments. We were also able to test comparisons between the PaO2 sensor and arterial blood gas (ABG) samples.

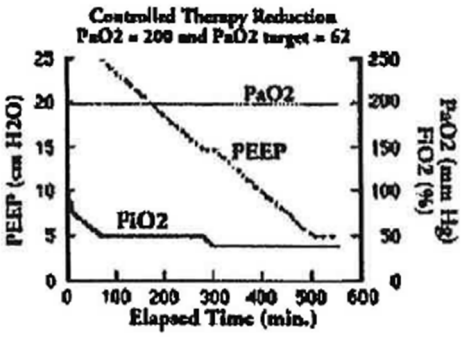

Figure 5. Controller's open loop response to "Supersatisfactory" patient PaO2.

Informed consent was obtained from 2 ARDS patients in the Shock/Trauma ICU at LDS Hospital for a clinical trial. The intra-arterial sensor was placed in a radial artery and calibrated following manufacturer's procedures. The closed-loop system was started to manage the patient's PEEP and FiO2 under continual observation of a trained respiratory therapist. Careful record was made of the patient's conditions and the performance of the controller.

RESULTS

Important results from bench testing in the laboratory are shown in figures 5 and 6. The controller's open loop response to "super-satisfactory" levels of PaO2 is shown in figure 5, where gradual reduction of oxygenation therapy is observed over a 9 hours period of time. The controller's open loop response to "threatening" PaO2 is illustrated in figure 6, where an aggressive rise in FiO2 and PEEP are observed over a relatively short period of time. These results demonstrate the controller's response to both high and low levels of patient oxygenation.

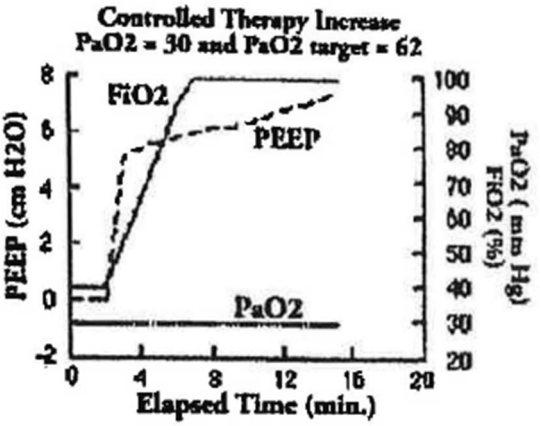

Figure 6. Controller's open loop response to "Threatening" patient PaO2.

In cases of PaO2 sensor failure, PEEP and FiO2 were maintained at prior values and warning signals were displayed. In cases of computer power failure and communication failure between the computer and ventilator, the ventilator switched to manual operation.

The controller performed as designed for all five animals and no adverse conditions were noted.

The closed-loop controller was used in clinical trials for nearly 184 hours with computer control of PEEP and FiO2 levels 84% of the time as summarized in Table 1. The remainder of the time the controller was by-passed for various procedures such as patient suctioning, PaO2 sensor calibration, and sensor replacement. A representative sample of the controller's response to a patient's PaO2 is shown in figure 7 where it is observed how the controller quickly responds with a rapid increase of FiO2 when the patient's PaO2 dips below the target level of 57. During periods when

the patient's PaO2 is above the target value, the controller responds with a gradual decrease in FiO2.

Table 1. Summary of controller usage during the clinical trial.

	Patient 1	Patient 2	Total
Total Hrs	23	161	184
Hrs Controlled	17	137	154
% Control	73	85	84

Twice the computer system unexpectedly went down due to electrical power interruption during thunderstorms. Control of patient therapy switched to manual settings on the ventilator, No adverse effects to patient therapy were noted.

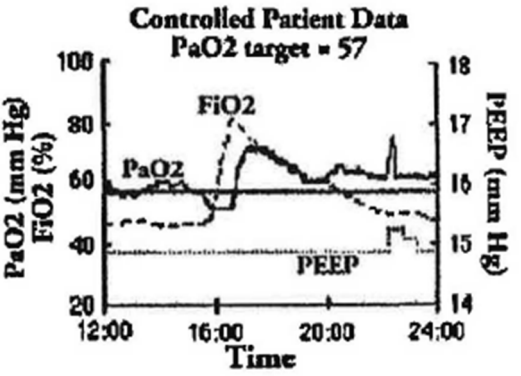

Figure 7; Typical patient data showing the controller's maintenance of PEEP and FiO2

DISCUSSION

The closed-loop controller performed as expected. If we look, however, at the collected PaO2 data, we can make several observations. Table 2 summarizes information regarding the patient's PaO2, the difference

between the patient's PaO2 and the target value, and the difference between the patient's PaO2 as measured with the Continucath monitor and blood samples processed with a Radiometer ABL3 blood gas machine in the hospital laboratory.

Table 2. PaO2 data collected from the clinical trial.

mean ± SD (mm Hg)	Patient 1	Patient 2	Total
PaO2 sensor	71.4±10.1	59.0±3.9	60.3±6.3
PaO2 sensor – Target	16.4±10.1	2.3±3.8	3.9±6.6
ABG – PaO2 sensor	4.1±12.7	1.5±5.5	2.1±7.7

Figure 8 shows a histogram of the PaO2 error, or the difference between the ABG and the PaO2 sensor. This information basically shows the accuracy, or calibration of the PaO2 monitor. Minimizing this error is important because accurate patient PaO2 readings are critical to appropriate therapy control. The error information shown in the histogram is somewhat misleading due to the fact that more ABG measurements are taken during the periods of time when the sensor is thought to be out of calibration. The controller is designed to sense conditions such as sensor failure, but is unable to detect gradual drifting over time. We also found the in-dwelling PaO2 sensor to be sensitive to arm position and temperature.

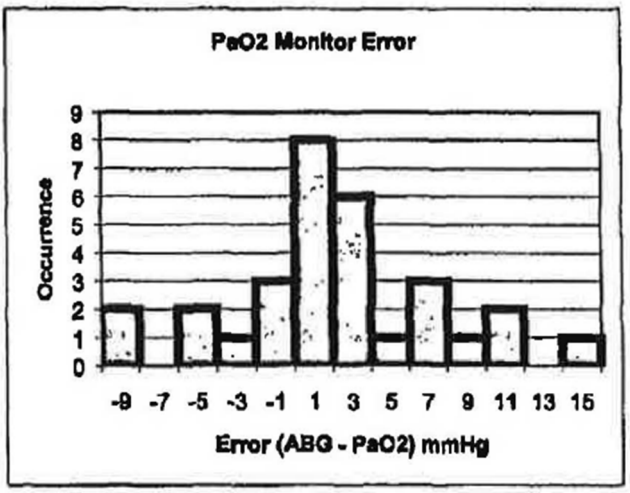

Figure 8 · Histogram of the PaO2 error in one patient.

CONCLUSIONS

Normal treatment of patients with ARDS includes intermittent sampling and measurement of the oxygen content in the patient's arterial blood. Based on these results, adjustments in ventilation therapy are made by the patient's physician or respiratory therapist. The interval between blood sample measurements is typically 4 to 8 hours. If the oxygen level in the patient's blood were to drop, it could be several hours before an appropriate response or adjustment in therapy is made. This new continuous closed-loop system would allow the computer to immediately respond to a drop in blood oxygenation, and reduce the chance of hazardous situations. This potential benefit seems to outweigh the potential risks, even though the impact of this closed-loop controller upon survival has not yet been formally evaluated. Our design of the closed-loop controller was found to be appropriate, reliable and

safe. Not once was the controller turned off or by-passed due to its control of oxygenation therapy. Our primary concern is the accuracy of the PaO2 readings that drive the controller. Our clinical trial was the first to use closed-loop control of PEEP and FIO2 in patients with ARDS.

ACKNOWLEDGMENTS

Hamilton Ventilators, Bonaduz, Switzerland; Pfizer Inc., New York, New York; LDS Hospital, Salt Lake City, Utah

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ANDERSON ET AL., *CLINICAL TRIAL OF A NON-LINEAR CLOSED-LOOP CONTROLLER FOR OXYGENATION DURING ARDS*, CRITICAL CARE MEDICINE, VOL 22, A188, JAN. 1994

TECHNICAL PAPER

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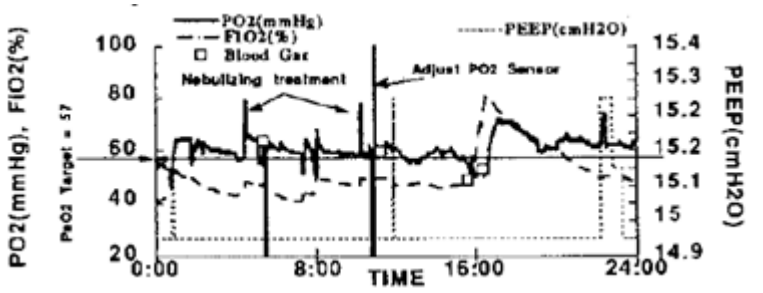
Positive end-expiratory pressure (PEEP) and high inspired oxygen fraction (FiO2) are frequently associated with undesirable side effects. Protocols designed to minimize the support levels while providing adequate oxygenation have been developed and tested clinically for over 40,000 hours in 200 ARDS patients resulting in over 60% survival(I). A system was designed based on these protocols which provides continuous closed-loop control of oxygenation. The purpose of this human clinical trial was to test the performance and safety of this controller.

Methods: The closed-loop control system consists of an in-dwelling PaO2 sensor (Pfizer Continucath) coupled to a Macintosh computer that continuously controls FiO2 and PEEP on a Hamilton Amadeus ventilator(2). Informed consent was obtained from 2 ARDS patients who received controlled therapy under the direction of their physician.

Result: Controller use is shown in the following table:

	Pat 1(Died)	Pat 2(Surv)	Total
Total Hrs	23.2	160.6	183.7
Hrs Controlled	17.0	136.8	153.8
% control	73.3	85.2	83.7

The controller was interrupted primarily for suctioning, PaO2 sensor calibration, and sensor replacement. An example of closed-loop control is illustrated in the following graph:



The PaO2, PaO2 controller error, and the difference between the Radiometer ABL3 blood gas machine and the PaO2 sensor is shown in the following table. (mean±SD mm Hg)

	Patient 1	Patient 2	Total
PaO2	71.4±10.1	59.0±3.9	60.3±6.3
PaO2-Target	16.4±10.1	2.3±3.8	3.9±6.6
ABG-sensor	4.1±12.7	1.5±5.5	2.1±7.7

Conclusions: This is the first clinical trial of a closed-loop controller designed to optimize both PEEP and FiO2 in patients with ARDS. The response of the closed-loop controller was found to be appropriate, reliable and safe. Future studies will be conducted to determine the efficacy of closed-loop control.

Grants: Hamilton Ventilators, Bonaduz, Switzerland.

References:

1. Morris AH, et al. Am Rev Resp Dis, 1992; 145(4): A184
2. East TD, et. al. Crit Care Med 1991; 19(4): S61.