Webcast Series

REDUCING COMPLICATIONS RELATED TO COVID-19: IT’S A FLUID SITUATION

Part 1: Using Goal-Directed Fluid Therapy to reduce time on mechanical ventilation

Thursday April 9

11 am EDT

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“70% to 80% of people who get intubated succumb to their infection.”

“Doctors are now experimenting with more fluids…what we should have is more literature that delineates what’s working and what’s not so doctors can take a more systematic, data-driven approach to these things.”

-Scott Gottlieb, MD 23rd Commissioner of the Food and Drug Administration

Today's Discussion

1. What do we know about COVID-19 complications?
2. What do the guidelines recommend for fluid management?
3. What is the evidence that supports use of GDFT?
4. How does this translate to reducing COVID-19 complications?
5. Where and how should the Argos CO monitor be deployed amid the current setting?

Jennifer Clarke, RN, BSN

Jennifer Clarke is currently the Regional Clinical Manager for Retia Medical. She has extensive experience as a Sepsis Coordinator, Telehealth nurse, and 20+ years bedside experience as a Surgical/Medical ICU nurse.

With this combined experience she has shared her subject matter expertise as a global speaker on sepsis and fluid optimization, and has served in key roles on multiple research teams.

Jennifer holds a BSN from Bradley University School of Nursing.

Harsha Agashe, PhD

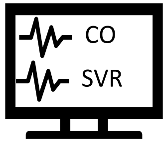
Harsha Agashe is currently the Product Manager of the Argos CO monitor at Retia Medical. He has extensive experience in cardiovascular physiological signal processing and was instrumental in developing Retia's MBA^{TM} algorithm.

He continues to lead clinical research and development of new algorithms at Retia Medical.

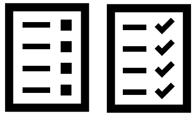
Harsha completed his doctorate in Electrical Engineering from the University of Houston.

Objectives

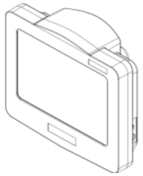
Discuss the impact of fluid assessment and administration on the treatment outcome for ARDS, ALI, AKI, septic shock and other complications associated with COVID-19



Describe the hemodynamic parameters that can guide an optimized fluid management strategy and identify the benefits of goal-directed fluid therapy (GDFT) within a critical care setting



Recognize the differences between currently available cardiac output monitoring technologies and describe the clinical advantages offered by the Multi-Beat Analysis (MBA™) Algorithm



Demonstrate use of the Argos Cardiac Output Monitor as part of a fluid-optimization protocol to reduce time on mechanical ventilation

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COVID-19 Outcomes

- On average, 48% of COVID-19 patients have Sepsis, Respiratory Failure, and/or ARDS. These conditions are also responsible for 97% of patient deaths[1]
- Optimized fluid resuscitation plays a vital role in patient outcomes for these conditions
- COVID-19 patients often remain on ventilators for 10 days or more, multiple times longer than a non-COVID-19 intubated patient[2]

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Treatments*				
Antibiotics	181 (95%)	53 (98%)	128 (93%)	0·15
Antiviral treatment	41 (21%)	12 (22%)	29 (21%)	0·87
Corticosteroids	57 (30%)	26 (48%)	31 (23%)	0·0005
Intravenous immunoglobin	46 (24%)	36 (67%)	10 (7%)	<0·0001
High-flow nasal cannula oxygen therapy	41 (21%)	33 (61%)	8 (6%)	<0·0001
Non-invasive mechanical ventilation	26 (14%)	24 (44%)	2 (1%)	<0·0001
Invasive mechanical ventilation	32 (17%)	31 (57%)	1 (1%)	<0·0001
ECMO	3 (2%)	3 (6%)	0	0·0054
Renal replacement therapy	10 (5%)	10 (19%)	0	<0·0001
Outcomes				
Sepsis	112 (59%)	54 (100%)	58 (42%)	<0·0001
Respiratory failure	103 (54%)	53 (98%)	50 (36%)	<0·0001
ARDS	59 (31%)	50 (93%)	9 (7%)	<0·0001
Heart failure	44 (23%)	28 (52%)	16 (12%)	<0·0001
Septic shock	38 (20%)	38 (70%)	0	<0·0001
Coagulopathy	37 (19%)	27 (50%)	10 (7%)	<0·0001
Acute cardiac injury	33 (17%)	32 (59%)	1 (1%)	<0·0001
Acute kidney injury	28 (15%)	27 (50%)	1 (1%)	<0·0001
Secondary infection	28 (15%)	27 (50%)	1 (1%)	<0·0001
Hypoproteinaemia	22 (12%)	20 (37%)	2 (1%)	<0·0001
Acidosis	17 (9%)	16 (30%)	1 (1%)	<0·0001
ICU admission	50 (26%)	39 (72%)	11 (8%)	<0·0001
ICU length of stay, days	8·0 (4·0–12·0)	8·0 (4·0–12·0)	7·0 (2·0–9·0)	0·41
Hospital length of stay, days	11·0 (7·0–14·0)	7·5 (5·0–11·0)	12·0 (9·0–15·0)	<0·0001
Time from illness onset to fever, days	1·0 (1·0–1·0)	1·0 (1·0–1·0)	1·0 (1·0–1·0)	0·16
Time from illness onset to cough, days	1·0 (1·0–3·0)	1·0 (1·0–1·0)	1·0 (1·0–4·0)	0·30
Time from illness onset to dyspnoea, days	7·0 (4·0–9·0)	7·0 (4·0–10·0)	7·0 (4·0–9·0)	0·51
Time from illness onset to sepsis, days	9·0 (7·0–13·0)	10·0 (7·0–14·0)	9·0 (7·0–12·0)	0·22
Time from illness onset to ARDS, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	10·0 (8·0–13·0)	0·65
Time from illness onset to ICU admission, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	11·5 (8·0–14·0)	0·88
Time from illness onset to corticosteroids treatment, days	12·0 (10·0–16·0)	13·0 (10·0–17·0)	12·0 (10·0–15·0)	0·55
Time from illness onset to death or discharge, days	21·0 (17·0–25·0)	18·5 (15·0–22·0)	22·0 (18·0–25·0)	0·0003
Duration of viral shedding after COVID-19 onset, days	20·0 (16·0–23·0)	18·5 (15·0–22·0)†	20·0 (17·0–24·0)	0·024

Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: Treatments and outcomes

1. Zhou F *et al* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*.395:1054-62. March 9, 2020
2. Bacon, John. A bridge between life and death: Most COVID-19 patients put on ventilators will not survive. USA Today. Apr 8, 2020.

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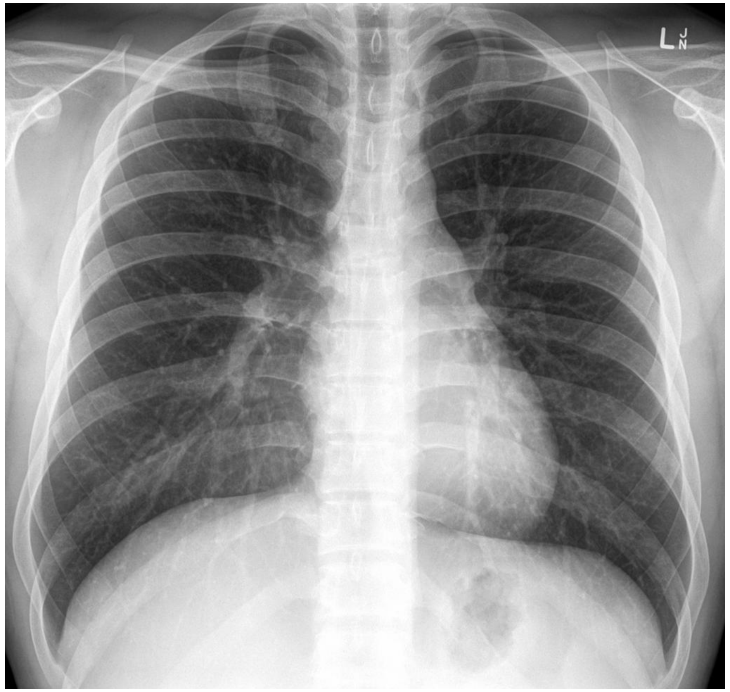
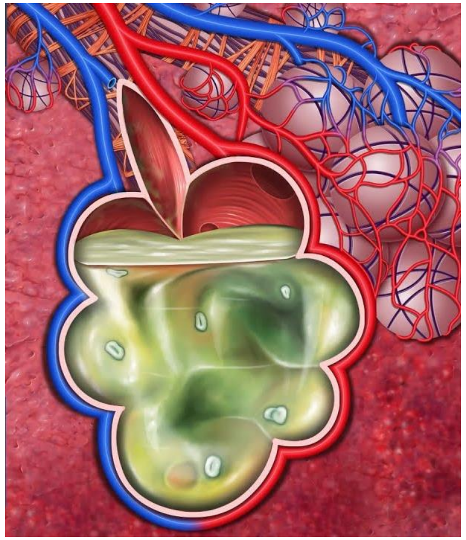
ARDS – A Common Denominator



Normal Chest X-Ray

Bilateral alveolar consolidation with panlobar change, with typical radiological findings of ARDS[1]

- Respiratory failure occurs in nearly 85% of cases of severe sepsis
- The most severe form of lung failure, ARDS, occurs in 40% of patients with sepsis



It is plausible that COVID-19 patients will respond to fluid similarly to other ARDS patients.

–SSC Guidelines on the Management of Critically Ill Adults with COVID-19

1. Lorente, E. COVID-19-Rapidly progressive acute respiratory distress syndrome https://radiopaedia.org/cases/covid-19-rapidly-progressive-acute-respiratory-distress-syndrome-ards

Treatment Guidelines

Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected
Interim guidance
13 March 2020
World Health Organization

"Use conservative fluid management in patients with SARI when there is no evidence of shock."

Remarks: "Patients with SARI should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation."[1]

"**Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation** based on local resources and experience[2]. These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation."

Surviving Sepsis Campaign

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

Recommendation: "For the acute resuscitation of adults with COVID-19 and shock, **we suggest using a conservative over a liberal fluid strategy**."

A 2017 meta-analysis of 11 RCTs (n=2,051 patients), adults and children with ARDS or sepsis managed according to a conservative fluid strategy in the post-resuscitation phase of critical illness had more ventilator-free days and shorter ICU stays than patients managed according to a liberal fluid strategy.[1]

1. Schultz MJ, Dunser MW, Dondorp AM, Adhikari NK, Iyer S, Kwizera A et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med. 2017;43(5):612-24. Epub 2017/03/30. doi: 10.1007/s00134-017-4750-z. PubMed PMID: 28349179.
2.Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77. Epub 2017/01/20. doi: 10.1007/s00134-017-4683-6. PubMed PMID: 28101605.

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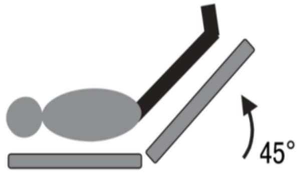
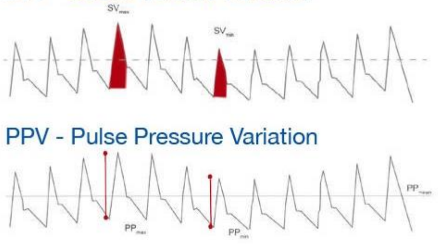
Dynamic Assessment with COVID-19 Pts

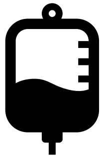


Potential Risks

- PLR
    - Patients present with severe hypoxia and shortness of breath which makes it difficult to lay patients flat
    - Requires multiple staff in room to perform the procedure. Exposure risk and limited PPE makes this a challenge



- PPV/SVV
    - Many COVID-19 pts are NOT in regular rhythm
    - PPV/SVV requires a minimum tidal volume (V_t) of $\geq$8 mL/kg[1], and COVID-19 patients have a lower recommended V_t[2]

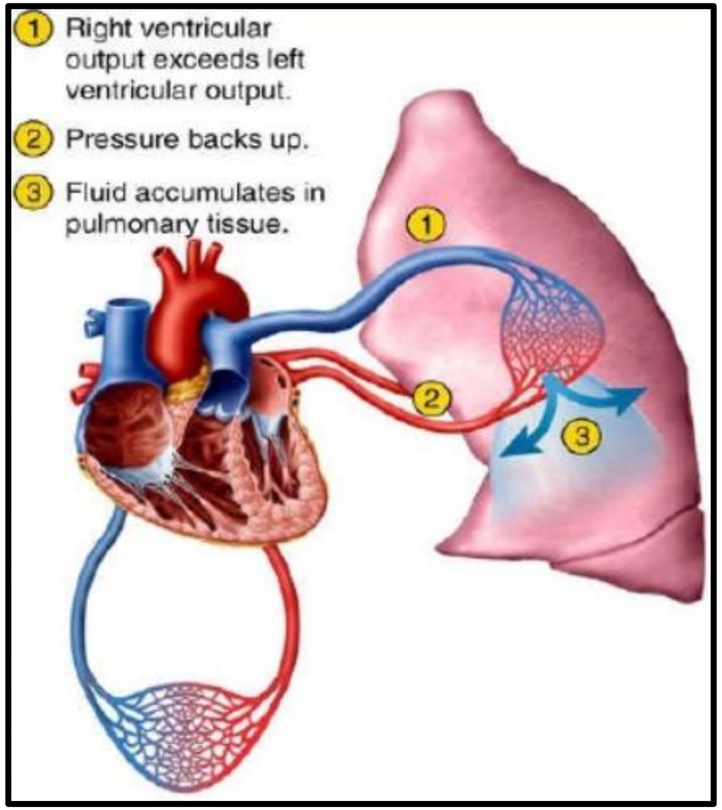


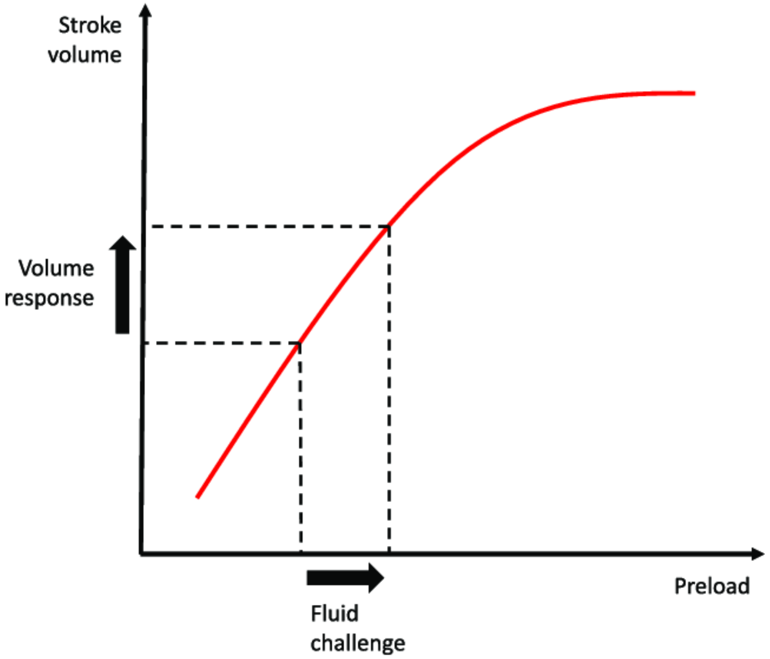
250-500 mL

Performing a fluid bolus of 250-500mL over 3-5 min would be more conducive to clinical workflow for COVID-19, given the resource constraints

1. Sanchez JIA *et al*. Use of Pulse Pressure Variation as Predictor of Fluid Responsiveness in Patients Ventilated with Low Tidal Volume: A Systematic Review and Meta-Analysis. *Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine*.14:1-10(2020)
2. Optimizing Ventilator Use during the COVID-19 Pandemic. U.S. Public Health Service Commissioned Corps. March 31,2020

Hemodynamics of Pulmonary Edema



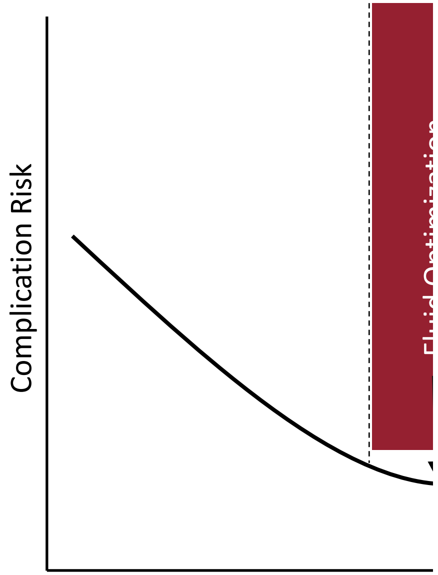


Fluid Optimization

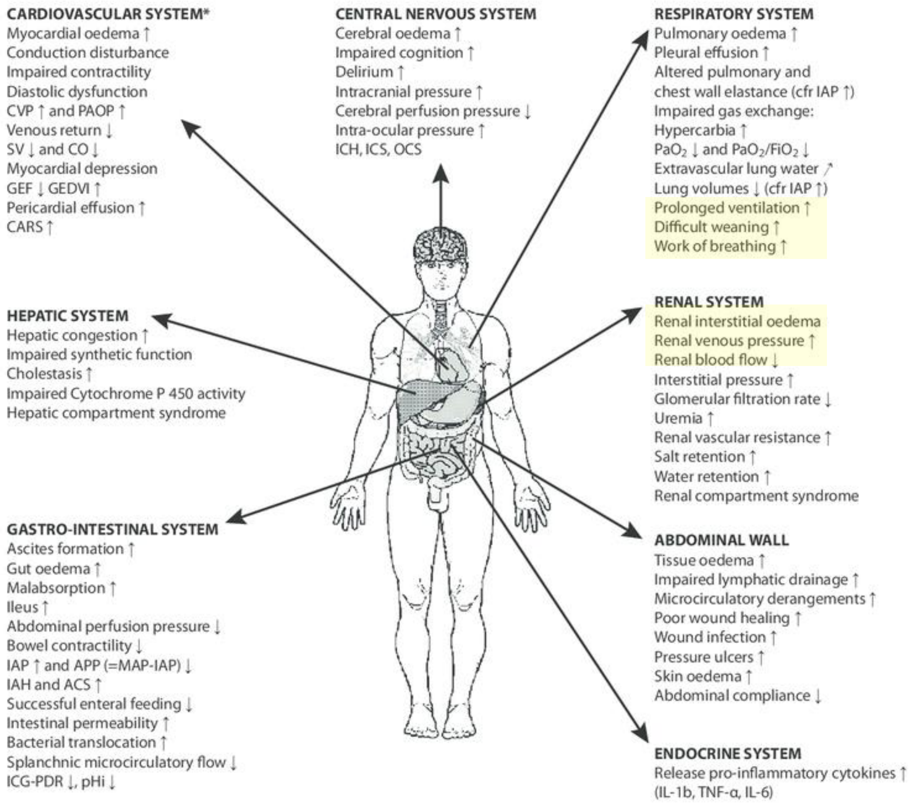
Restrictive Fluid Approach

Risks of hypovolemia:

- Tachycardia
- Hypotension
- Renal Failure
- Tissue Hypoperfusion
- Multiple Organ Failure



Effects of **Fluid Overload** on End-Organ Function



Malbrain, Manu & Marik, Paul & Witters, Ine & Cordemans, Colin & Kirkpatrick, Andrew & Roberts, Derek & Regenmortel, Niels. (2014). Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: A systematic review with suggestions for clinical practice. Anaesthesiology intensive therapy. 46. 361-80. 10.5603/AIT.2014.0060.

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Fluid Balance and Time on Mechanical Ventilation

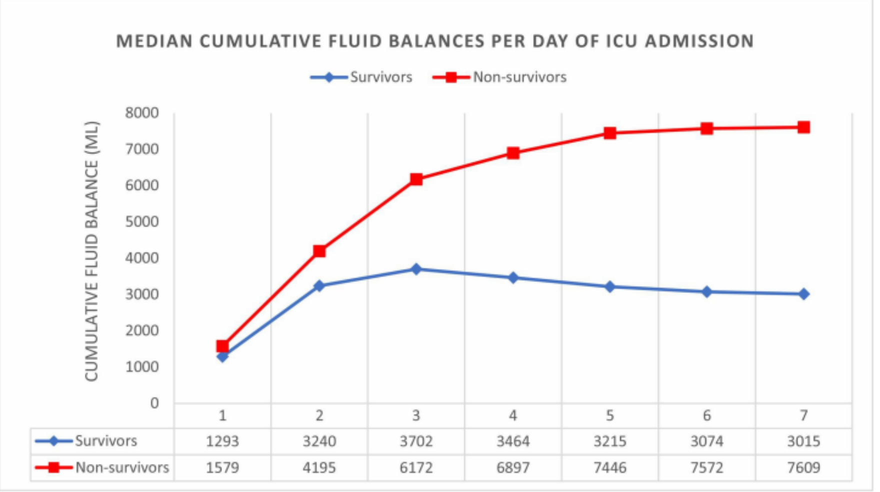

Fig 1. Median cumulative fluid balance in the first 7 days of ICU admission in survivors and non-survivors. Survival was based on 28-day mortality. Survivors are marked blue, non-survivors are marked red. On the Y-axis the cumulative fluid balance in mL is found. On the X-axis days of ICU admission with corresponding median cumulative fluid balances (mL) for survivors and non-survivors.

	Group I < 0 **L** **N = 123**	**Group II** **0–3.5 L** **N = 177**	**Group III** **3.5-8L** **N = 151**	**Group IV** ≥ 8 **L** **N = 149**	**P-value**
Mortality–n (%)					
28-day mortality	11 (8.9)[II,III,IV]	34 (19.2)[I, IV]	40 (26.5)[I, IV]	71 (47.7)[I,II,III]	*<0.001*
90-day mortality	16 (13.0)[II,III,IV]	50 (28.2)[I, IV]	52 (34.4)[I, IV]	84 (56.4)[I,II,III]	*<0.001*
ICU mortality	5 (4.1)[III, IV]	15 (8.5)[III, IV]	33 (21.9)[I, II, IV]	57 (38.3)[I, II, III]	*<0.001*
Ventilation					
Ventilator-free days on day 28	25.1 [20.8–26.6][II, III, IV]	24.3 [10.4–26.0][I, III, IV]	19.2 [0.00–25.1][I, II, IV]	0.00 [0.00–19.5][I, II, III]	*<0.001*
Weaned off ventilator by day 28	107 (87.0)[III, IV]	139 (78.5)[IV]	106 (70.2)[I, IV]	70 (47.0)[I, II, III]	*<0.001*
Duration of mechanical ventilation–hours	62.0 [31.5–136][III, IV]	80.0 [39.0–136][III, IV]	132 [61.0–257][I, II, IV]	189 [101–358][I, II, III]	*<0.001*
Length of stay–days					
ICU length of stay	5.03 [3.05–8.65][III, IV]	5.45 [3.49–8.32][III, IV]	8.39 [4.65–12.8][I, IV]	11.6 [6.35–20.7][I, II, III]	*<0.001*
Hospital length of stay	17.0 [10.0–32.5][IV]	15.0 [9.00–35.0][IV]	21.0 [12.0–38.0]	28.5 [14.0–45.0][I, II]	*0.004*

Values indicated with n are number of patients. Medians are presented with interquartile ranges between square brackets. Significantly differing groups ($p<0.05$) are displayed in superscript. ICU denotes Intensive Care Unit.

- Dose-response relationship between cumulative fluid balance and duration of mechanical ventilation
- Higher cumulative fluid balance is independently associated with increased risk of mortality, longer ICU stay, and longer time on ventilation in patients with ARDS

van Mourik N, Metske HA, Hofstra JJ, Binnekade JM, Geerts BF, Schultz MJ, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: An observational cohort study. PLoS ONE14(10):e0224563.2019

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Goal-Directed Fluid Therapy (GDFT)

Goal-Directed Therapy – A technique used in critical care medicine that utilizes intensive monitoring and aggressive management of hemodynamics to help guide clinicians in the administration of fluids, vasopressors, inotropes, or other treatments to patients with a high risk of morbidity and mortality

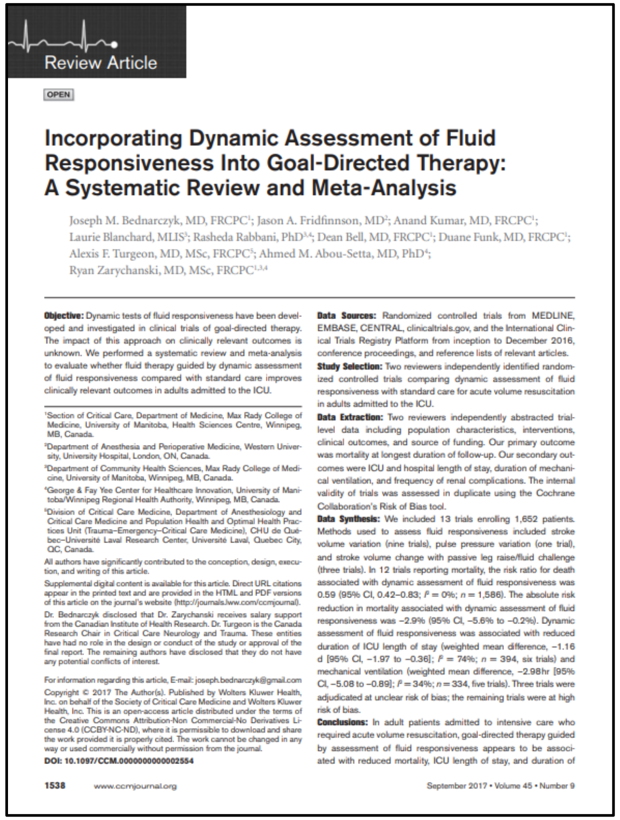
- A 2017 systematic review and meta-analysis of 13 RCTs (n=1,652) examined the effect of dynamic assessment of fluid therapy on outcomes

- The use of dynamic assessment to guide fluid therapy was found to:

  ⬇ Reduce Mortality

  ⬇ ICU Length of Stay

  ⬇ Duration of Mechanical Ventilation



Review Article

OPEN

Incorporating Dynamic Assessment of Fluid Responsiveness Into Goal-Directed Therapy: A Systematic Review and Meta-Analysis

Joseph M. Bednarczyk, MD, FRCPC[1]; Jason A. Fridfinnson, MD[2]; Anand Kumar, MD, FRCPC[1]; Laurie Blanchard, MLIS[3]; Rasheda Rabbani, PhD[3,4]; Dean Bell, MD, FRCPC[1]; Duane Funk, MD, FRCPC[1]; Alexis F. Turgeon, MD, MSc, FRCPC[5]; Ahmed M. Abou-Setta, MD, PhD[4]; Ryan Zarychanski, MD, MSc, FRCPC[1,3,4]

Objective: Dynamic tests of fluid responsiveness have been developed and investigated in clinical trials of goal-directed therapy. The impact of this approach on clinically relevant outcomes is unknown. We performed a systematic review and meta-analysis to evaluate whether fluid therapy guided by dynamic assessment of fluid responsiveness compared with standard care improves clinically relevant outcomes in adults admitted to the ICU.

Data Sources: Randomized controlled trials from MEDLINE, EMBASE, CENTRAL, clinicaltrials.gov, and the International Clinical Trials Registry Platform from inception to December 2016, conference proceedings, and reference lists of relevant articles.

Study Selection: Two reviewers independently identified randomized controlled trials comparing dynamic assessment of fluid responsiveness with standard care for acute volume resuscitation in adults admitted to the ICU.

Data Extraction: Two reviewers independently abstracted trial-level data including population characteristics, interventions, clinical outcomes, and source of funding. Our primary outcome was mortality at longest duration of follow-up. Our secondary outcomes were ICU and hospital length of stay, duration of mechanical ventilation, and frequency of renal complications. The internal validity of trials was assessed in duplicate using the Cochrane Collaboration's Risk of Bias tool.

Data Synthesis: We included 13 trials enrolling 1,652 patients. Methods used to assess fluid responsiveness included stroke volume variation (nine trials), pulse pressure variation (one trial), and stroke volume change with passive leg raise/fluid challenge (three trials). In 12 trials reporting mortality, the risk ratio for death associated with dynamic assessment of fluid responsiveness was 0.59 (95% CI, 0.42–0.83; $I^2 = 0\%$; $n = 1,586$). The absolute risk reduction in mortality associated with dynamic assessment of fluid responsiveness was –2.9% (95% CI, –5.6% to –0.2%). Dynamic assessment of fluid responsiveness was associated with reduced duration of ICU length of stay (weighted mean difference, –1.16 d [95% CI, –1.97 to –0.36]; $I^2 = 74\%$; $n = 394$, six trials) and mechanical ventilation (weighted mean difference, –2.98 hr [95% CI, –5.08 to –0.89]; $I^2 = 34\%$; $n = 334$, five trials). Three trials were adjudicated at unclear risk of bias; the remaining trials were at high risk of bias.

Conclusions: In adult patients admitted to intensive care who required acute volume resuscitation, goal-directed therapy guided by assessment of fluid responsiveness appears to be associated with reduced mortality, ICU length of stay, and duration of

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[3]Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada.

[4]George & Fay Yee Center for Healthcare Innovation, University of Manitoba/Winnipeg Regional Health Authority, Winnipeg, MB, Canada.

[5]Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine and Population Health and Optimal Health Practices Unit (Trauma–Emergency–Critical Care Medicine), CHU de Québec–Université Laval Research Center, Université Laval, Quebec City, QC, Canada.

All authors have significantly contributed to the conception, design, execution, and writing of this article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Bednarczyk disclosed that Dr. Zarychanski receives salary support from the Canadian Institute of Health Research. Dr. Turgeon is the Canada Research Chair in Critical Care Neurology and Trauma. These entities have had no role in the design or conduct of the study or approval of the final report. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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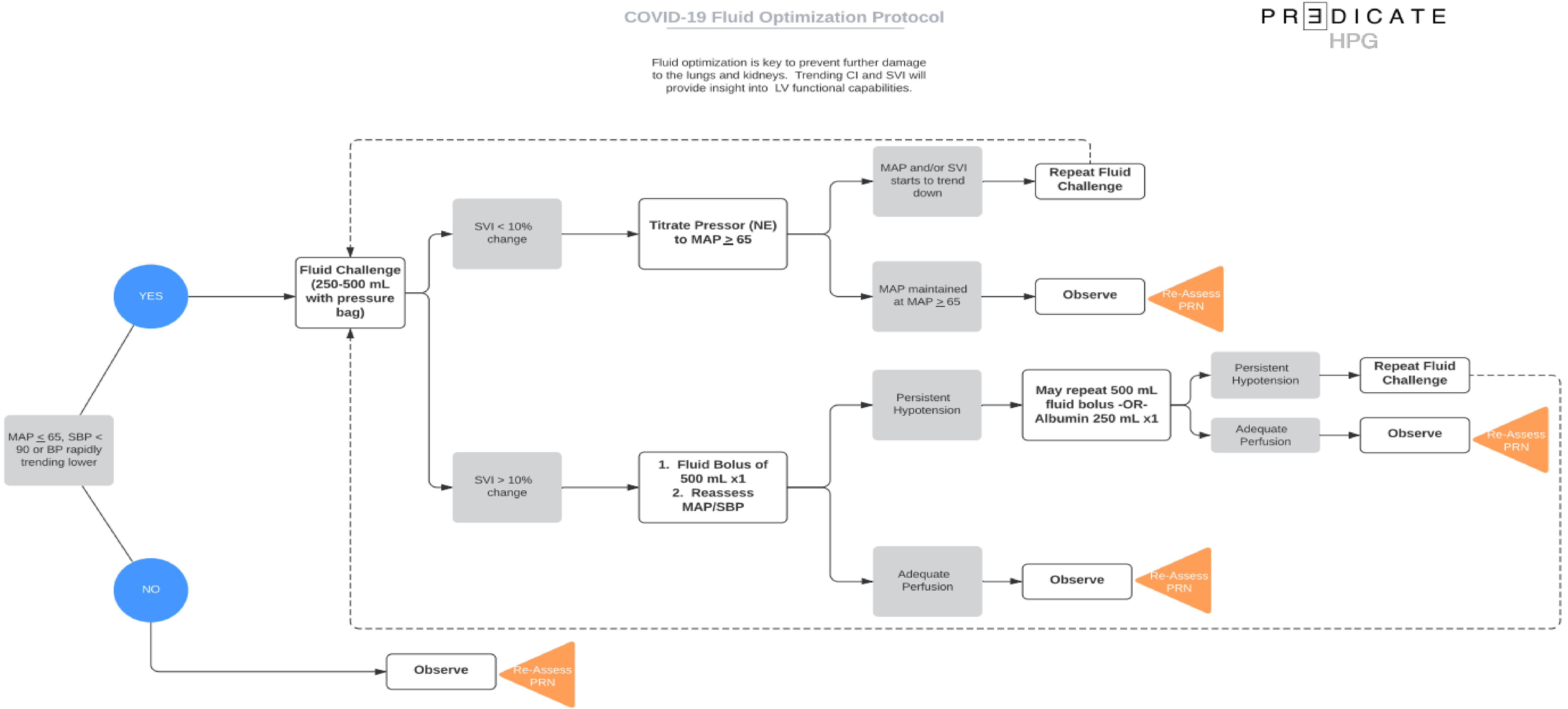
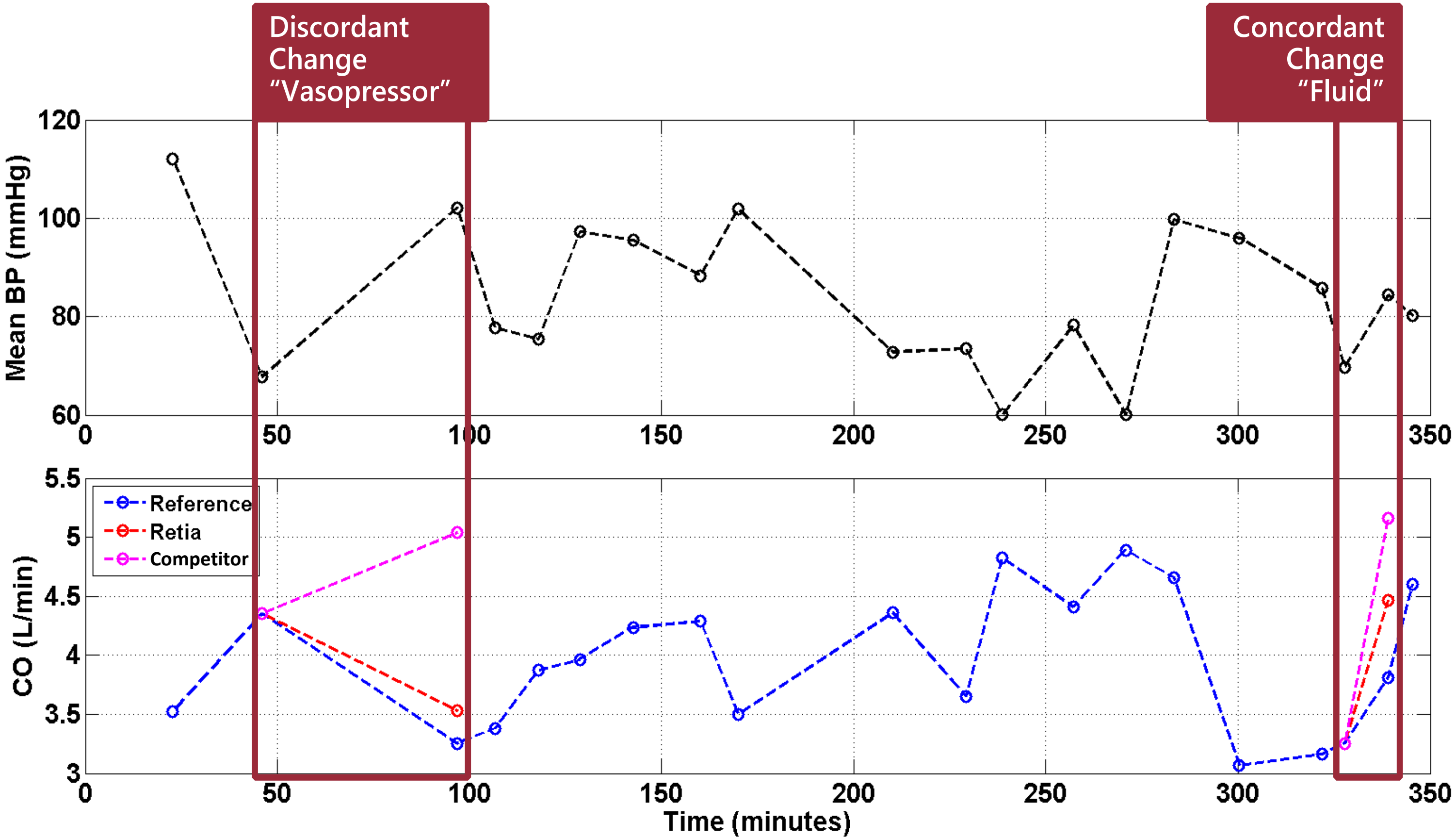
Fluid Optimization Protocol



Technology and Clinical Application

The Need for Consistent Accuracy

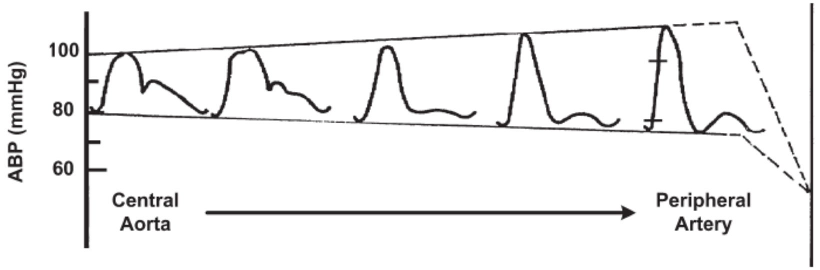


Why was the Multi-Beat Analysis (MBA™) Algorithm created?

The limited ability of single-beat technologies to *consistently* track changes in CO is largely influenced by changes in vasomotor tone (i.e. peripheral vasoconstriction)

Case Study: 66-year-old female, liver transplant at Columbia University Irving Medical Center

The MBA™ Algorithm



- Other hemodynamic monitors analyze one heartbeat at a time and cannot distinguish if an increase in pulse pressure or stroke volume was the result of fluid administration or from vasopressors (increased systemic vascular resistance)
- The Argos CO monitor, which uses the MBA™ algorithm analyzes multiple heartbeats to create an accurate model of circulation
- Automatically calculates the model parameters that generate an observed multi-beat blood pressure signal
- The result is an algorithm that is accurate when needed the most:
  - During low CO states, a situation commonly seen with COVID-19 patients
  - When CO is changing, important when tracking decompensation in COVID-19 patients. Provides accuracy in tracking SVI/CI and is key for fluid optimization.

Refresh Rate is every 5 secs, analyzing 20 secs of the BP waveform

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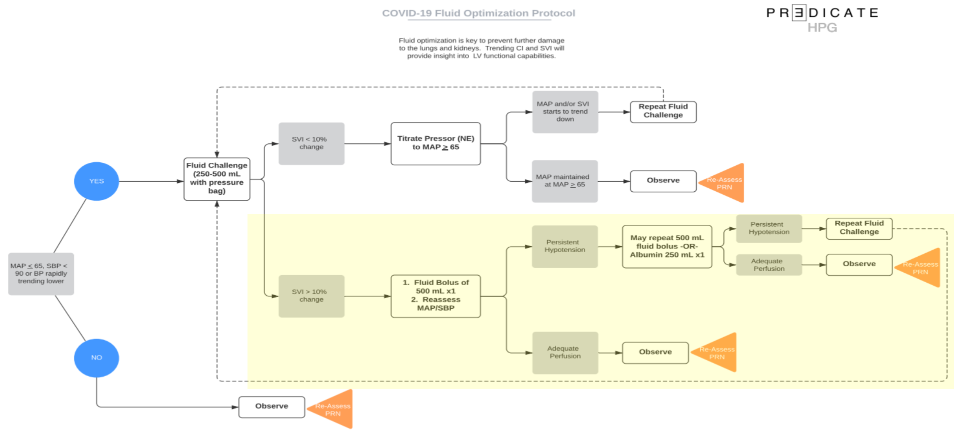
Utilizing the MBA™ Algorithm in a Clinical Scenario



- MAP=55
- Baseline SVI=25
- 10% increase in SVI after fluid challenge
- SVI=28

Order written for 250mL to be given over 3-5 min

- Re-assess SVI with Argos CO monitor
- SVI=29, greater than a 10% increase from previous
- Pt still hypotensive with MAP=60
- Order written for 500mL bolus
- SVI=29 and increases >10% after fluid bolus

- SVI=33 and MAP=68
- Continue to monitor
- If patients SVI starts to trend down and/or MAP drops again, repeat protocol

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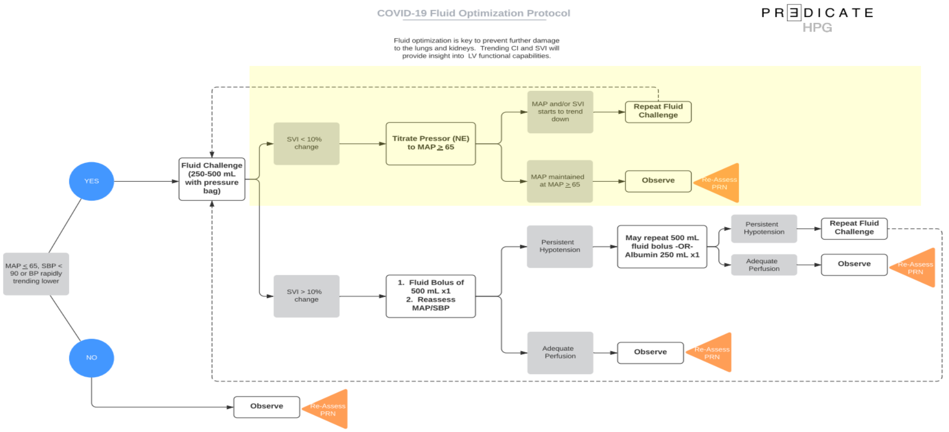
Utilizing the MBA™ Algorithm in a Clinical Scenario

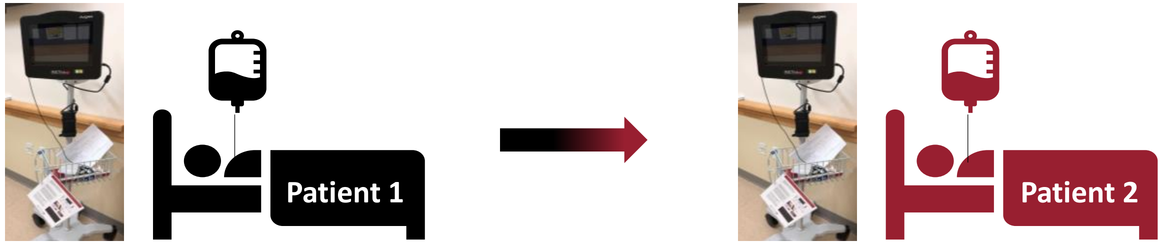


- MAP of 55
- SVI=25
- 10% increase in SVI after fluid bolus
- 250mL bolus ordered
- SVI=23 indicating patient did not respond to the fluid bolus and pressor will be started

- Pressor of choice started and titrate to achieve MAP=65
- If MAP falls again, then intervene with fluid bolus

Deploying the Argos Monitor in Your ICU

Easy setup to *quickly* meet the monitoring needs of each COVID-19 patient



Compatible with different patient monitors

Argos Monitor input

Enter in Patient Data

Hemodynamic profile in seconds

1

2

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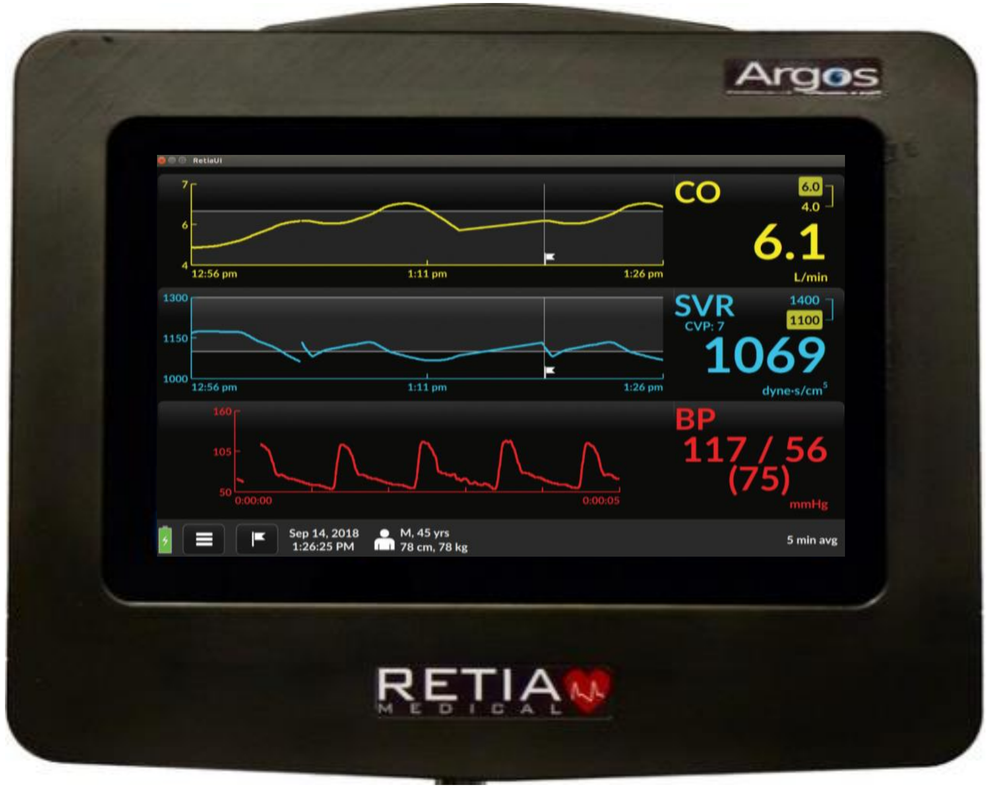
Argos CO Monitor with MBA™ Algorithm



CO | CI

SV | SVI

SVR | SVRI

BP | PPV

MAP | HR

Key Takeaways

More than 50% of COVID-19 patients experience respiratory failure and are at a high risk requiring prolonged mechanical ventilation[1,2]

Fluid under/over-resuscitation can exacerbate existing gas-exchange abnormalities and extend the requirement for mechanical ventilation

A goal-directed fluid management strategy guided by SVI/CI has been shown to decrease time on mechanical ventilation[3]

The Argos CO monitor with Multi-Beat Analysis (MBA™) resolves the limitations of other pulse contour technologies by analyzing multiple heart beats and can provide a full hemodynamic profile within seconds using an existing arterial line

Continued focus on interventions to reduce duration of mechanical ventilation are both clinically and operationally significant during a time when ventilator demand is anticipated to exceed supply

1 Zhou F *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* March 11, 2020.
2 Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. *Critical Care Medicine.* 2010; 38:1947–53.
3 Data on file.

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Thank you for your attention. Questions?

For additional information, contact info@retiamedical.com