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Ten recent advances that could not have come about without applying physiology

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Physiology forms the basis of our understanding of disease and most treatments and the means to assess response to treatment. Thus, almost all new therapies are based on physiology. However, ten recent advances clearly reflect this realization well (Table 1). By applying these advances at the bedside the clinician is forced to consider the patient's physiologic state when making decisions.

1. Assessing fluid responsiveness

Fluid responsiveness assesses preload reserve not preload. Static estimates of cardiac preload do not predict preload responsiveness [1]. Increasing stroke volume (SV) in response to increasing preload defines preload responsiveness. Both positive-pressure breathing and passive leg raising (PLR), by transiently altering preload, can be used to predict volume responsiveness without giving fluids. Arterial pulse pressure variation (PPV) or left ventricular (LV) SV variation (SVV) >10–13 % in patients on positive-pressure ventilation (Vt ≥8 ml/kg) or an increase in cardiac output >10 % to PLR in any subject identifies volume responders [2, 3]. Similarly, transient end-tidal expired CO_2 increases can be used as a surrogate for changes in cardiac output in response to PLR [3].

2. Estimating cardiac output and left ventricular stroke volume from arterial pressure

Since arterial pulse pressure (PP) is a function of LV SV plus ventriculo-arterial coupling properties, numerous devices now estimate cardiac output from the arterial pressure signal. Since the determinants of arterial PP are complexed by changes in arterial tone, impedance, inertance, and contractility, the various devices have differing degrees of accuracy depending on pathologic state [4].

3. Choice of fluids for resuscitation

The composition of intravenous fluids affects fluid and electrolyte balance, and in turn acid–base balance, in non-

Table 1 Ten advances needing physiology

1	Assessment of fluid responsiveness
2	Estimating cardiac output and left ventricular stroke volume from arterial pressure
3	Choice of fluids for resuscitation
4	Dialysis and ultrafiltration may cause hypotension but for pulse pressure (PP) different reasons
5	Plateau pressure and tidal volume limits to minimize lung injury
6	Prone positioning to minimize lung injury and maximize gas exchange
7	Limiting airway pressure to optimize cardiovascular function
8	Optimizing PEEP according to the severity of lung injury
9	Extracorporeal gas exchange may be the future
10	Small changes in renal function may indicate significant kidney injury

intuitive but predictable ways. In large volumes, isotonic saline solution causes hyperchloremia and acidosis [5]. Serum potassium increases more with saline than lactated Ringer's owing to the physiologic effect of shifting potassium from the cells when pH falls [6]. Crystalloids rapidly move from the intravascular space into total body water. This restores total body deficits when present, but may produce fluid overload when used excessively. Fluids are physiologically active drugs that have a wide range of effects on both the endothelium and organs. The widespread availability of alternatives to normal saline with varied composition is a direct result of advances in the understanding of physiology.

4. Dialysis and ultrafiltration may both cause hypotension but for different reasons

All forms of ultrafiltration remove intravascular fluid and cause relative hypovolemia. Vascular refill rate from the interstitium minimizes the hypovolemia up until cardiovascular collapse. Regrettably, cardiovascular collapse during dialysis is commonplace. Newer forms of dialysis such as continuous renal replacement therapy (CRRT) and slow low-efficiency dialysis minimize this cardiovascular stress by allowing for a more gradual fluid removal, causing less ischemia-induced end-organ injury [7]. However, hemodialysis may cause hemodynamic instability even when no fluid is removed if rapid solute removal from the blood compartment causes water to move into the tissue (i.e., disequilibrium syndrome) [8]. CRRT and other slower modes of RRT avoid rapid shifts and generally result in less hemodynamic compromise [9].

5. Plateau pressure and tidal volume limits to minimize ventilator-induced lung injury (VILI)

Large tidal volumes and high distending pressures are injurious to both injured and normal lungs, thereby increasing mortality [10]. The goal is to minimize alveolar wall stress and strain (or deformation) while still providing reasonable gas exchange despite regional differences in lung compliance. Thus, limiting plateau pressure (<28 cmH_2O) and tidal volume (≤ 6 ml/kg) minimizes regional overdistention and improves survival in mechanically ventilated patients and is consistent with the fact that total lung capacity is reached at approximately 30 cmH_2O [11].

6. Prone positioning to minimize lung injury and maximize gas exchange

Regional pulmonary blood flow and alveolar ventilation are dependent on regional differences in vascular flow direction, chest wall compliance, and gravity. Prone positioning allows the largest region of lung that is in the posterior thorax to remain aerated while not impeding pulmonary blood flow. The predominance of the posterior pulmonary vascular perfusion is preserved with prone positioning, and not influenced by gravity. This explains its effects on gas exchange. Prone position also stiffens the chest wall, reducing its compliance and allowing a more homogeneous distribution of ventilation protecting the lungs from overdistention [12] and also avoids cardiac compression of the lungs.

7. Limiting airway pressures to optimize cardiovascular function

Lung overdistention increases pulmonary vascular resistance. If generalized, inspiratory-hold plateau pressure increases, which can make the alveolar pressure higher than the venous or arterial capillary pressure (zone 2 and zone 1), leading to pulmonary hypertension, ultimately causing acute cor pulmonale. By limiting plateau pressure, either through limitation of positive end-expiratory pressure (PEEP), tidal volume, or both, marked reductions in the incidence of acute cor pulmonale coupled with increases in cardiovascular responsiveness occur [13].

8. Optimizing the PEEP according to the severity of lung injury

The risks associated with lung unit opening and closure explain the need for higher PEEP in severe ARDS [14], whereas the deleterious physiologic effects of PEEP are due to overdistention; thus higher levels of PEEP in patients should be reserved for patients having a substantial degree of alveolar instability (i.e., highly recruitable patients). PEEP titration to optimize both compliance and oxygenation may be used to select PEEP [15].

9. Extracorporeal gas exchange may be the future

Extracorporeal therapies such as ECMO and $ECCO_2R$ allow lung healing or minimize the impact of VILI [16]. Although the efficacy of ECMO to influence outcomes from ARDS still needs confirmation, $ECCO_2R$ may reduce the risk of VILI or possibly avoiding intubation of hypercapnic patients [17]. Combining the physiology of gas exchange and acid–base physiology may soon lead to additional modes of support such as bicarbonate removal as a form of $ECCO_2R$.

10. Small changes in renal function may indicate significant kidney injury

Humans have substantial renal functional reserve. A loss of more than 50 % renal function is needed to see a rise in serum creatinine. Thus, small changes in serum creatinine can indicate substantial kidney damage with resultant long-term adverse outcomes [18], prompting extensive reevaluation of the epidemiology of acute kidney injury, approval of biomarkers, and transforming how we are

evaluating treatments. Even transient episodes of oliguria appear to be associated with long-term hazard [19].

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References

1. Michard F, Teboul JL (2002) Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 121:2000–2008
2. Michard F, Bossat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
3. Monnet X, Bataille A, Magalhaes E, Barrois J, Le Corre M, Gosset C, Guerin L, Richard C, Teboul JL (2013) End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. Intensive Care Med 39:93–100
4. Guarracino F, Ferro B, Morelli A, Baldisseri R, Pinsky MR (2014) Arterio-ventricular decoupling in human septic shock. Crit Care 18(2):R80
5. Scheingraber S, Rehm M, Sehmisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 90:1265–1270
6. Mahnensmith R, Thier SO, Cooke CR et al (1979) Effect of acute metabolic acidemia on renal electrolyte transport in man. Metab Clin Exp 28:831–842
7. Rabindranath K, Adams J, Macleod AM (2007) Intermittent versus continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev CD003773
8. Wakim KG (1969) The pathophysiology of the dialysis disequilibrium syndrome. Mayo Clin Proc 44:406–429
9. Schortgen F, Soubrier N, Delclaux C, Thuong M, Girou E, Brun-Buisson C, Lemaire F, Brochard L (2000) Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: usefulness of practice guidelines. Am J Respir Crit Care Med 162:197–202
10. Neto AS, Cardoso SO, Manetta JA, Pereira VGM, Espósito DC, Pasqualucci MDOP, Damasceno MCT, Schultz MJ (2012) Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 308:1651–1659
11. Rahn H, Otis AB, Chadwick LE, Fenn WO (1946) The pressure–volume diagram of the thorax and lung. Am J Physiol 146:161–178
12. Pelosi P, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, Gattinoni L (1998) Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 157:387–393
13. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, Beauchet A, Jardin F (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 29:1551–1555
14. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Gattinoni L (2008) Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 178:346–355
15. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NK, Pinto R, Fan E, Brochard LJ, Granton JT, Mercat A, Marie Richard JC, Chretien JM, Jones GL, Cook DJ, Stewart TE, Slutsky AS, Meade MO, Ferguson ND (2014) Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and express trials. Am J Respir Crit Care Med 190:70–76
16. Cove ME, MacLaren G, Federspiel WJ, Kellum JA (2012) Bench to bedside review: extracorporeal carbon dioxide removal, past present and future. Crit Care 16:232
17. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM (2009) Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology 111:826–835
18. Linder A, Fjell C, Levin A et al (2014) Small acute increases in serum creatinine are associated with decreased long term survival in the critically Ill. Am J Respir Crit Care Med 189:1075–1081
19. Kellum JA, Sileanu FE, Murugan R et al (2015) Classifying acute kidney injury by urine output versus serum creatinine. J Am Soc Nephrol. doi: 10.1681/ASN.2014070724