What is new in respiratory monitoring?

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Abstract
This paper provides a review of a selection of papers published in the Journal of Clinical Monitoring and Computing in 2020 and 2021 highlighting what is new within the field of respiratory monitoring. Selected papers cover work in pulse oximetry monitoring, acoustic monitoring, respiratory system mechanics, monitoring during surgery, electrical impedance tomography, respiratory rate monitoring, lung ultrasound and detection of patient-ventilator asynchrony.

Keywords Respiratory monitoring · Mechanical ventilation · Oximetry · Respiratory mechanics · Lung imaging · Pulmonary ventilation

1 Introduction
In the period 2020-21, the Journal of Clinical Monitoring and Computing (JCMC) published a wide variety of papers within respiratory monitoring. Here we provide brief reviews of several selected papers, each of which we consider illustrates what is new in respiratory monitoring. Not surprisingly, many of these new advances concern monitoring applications in mechanically ventilated patients in the intensive care unit; the current trend is to promote spontaneous breathing efforts in ventilated patients, but this introduces new therapeutic challenges and monitoring requirements. An increasing focus in recent years has also been on the use of respiratory monitoring to personalize mechanical ventilation during surgery, as well as the continued search for reduced invasiveness in measurement and imaging technologies for intensive care and surgical patients both during and following liberation from mechanical ventilation. Highlighted papers feature explorations of new applications for existing measurement parameters, testing and improving the performance of existing measurement technologies, and proof of concept testing of new prototype technologies.

2 Acoustic monitoring of airway patency
Invasive mechanical ventilation as applied during surgery or intensive care requires insertion of an endotracheal tube into the patient’s trachea and inflation of an endotracheal tube cuff in order to permit positive pressure ventilation and prevent aspiration. However, the cuff also effectively prevents natural clearance of airway secretions by mechanically blocking mucus flow. Maintenance of airway patency and prevention of complications associated with secretion build up below the cuff requires endotracheal suctioning [1]. However, as endotracheal suctioning is associated with side-effects and pain, current guidelines stipulate that it should be performed only on indication [1, 2]. The need for endotracheal suctioning is usually evaluated based on the inspection of waveforms presented by the mechanical ventilator, changes in oxygenation, and patient airway and respiratory status [1].

Moon et al. [3] present a new acoustic based monitoring device to assist in evaluation of tracheal accumulation of secretions. In a retrospective analysis, they performed power
spectral analysis of sound recordings from an oesophageal stethoscope in 20 surgical patients split between 9 with documented intraoperative removal of secretion and 11 with documentation of no respiratory disease as well as no secretions during surgery. They found significant differences in signal power within different frequency bands as well as ratios of frequency band power to total power when comparing recordings with secretion to recordings in control patients with no secretions. A reduction in power following removal of secretion was observed in the frequency range 80–500 Hz although not to the level recorded in control patients. The highest area under the receiver operating characteristic curve obtained with various power ratios showed a convincing sensitivity of 1.000 and specificity of 0.889 for discrimination of sounds generated by tracheal secretions from normal breath sounds.

The problem of secretion build-up below the cuff is exacerbated in the intensive care unit where patients can be on mechanical ventilation for long durations. In this setting, another acoustic monitoring device has previously been prospectively evaluated in a randomized controlled trial comparing endotracheal suctioning by device indication versus a control group where endotracheal suctioning was performed 3 times a day [4]. This study found that fewer endotracheal suctioning as well as unnecessary endotracheal suctioning were performed in the suctioning by acoustic indication group, although it appears that the commercial device used in this study is no longer available. It would be interesting to see if the new device and method presented in a small preliminary study by Moon et al. [3] could be further developed for practical use in surgery as well as in the intensive care setting for detection of secretion build up.

3 Respiratory system mechanics in the critically ill

The mechanical properties of the respiratory system are often compromised in lung disease and thus can serve as invaluable biomarkers of disease severity and response to treatment [5]. Indeed, research in this area goes back many decades and is still being actively pursued as monitoring methods and our understanding of pulmonary pathophysiology become more refined. The monitoring methods themselves generally involve the measuring of pressures, air flows, and volumes at appropriate sites such as the mouth and in the esophagus. The mechanical characteristics of monitoring systems and how they interface with the patient are thus also of central clinical interest. Not surprisingly, the JCMC has featured a number of papers focused on aspects of respiratory system mechanics and its measurement.

One of these papers [6] reported a novel method for estimating transpulmonary pressure using fluctuations in central venous pressure. Transpulmonary pressure represents the key stress applied across the lungs, either during spontaneous breathing or mechanical ventilation, that determines how it inflates and deflates during respiration. Obtaining transpulmonary pressure in an intact patient requires measuring pleural pressure in order to separate the pressure drop across the entire respiratory system into its component across the lung (i.e., transpulmonary pressure) and the remainder comprising the pressure drop across the chest wall. Clinically, pleural pressure is equated to esophageal pressure, which conveniently can be measured with the use of an esophageal balloon [7]. While this technique is very safe, it can nevertheless be awkward to apply and is somewhat distasteful for the patient. There has thus been ongoing interest in alternative ways of estimating pleural pressure, and thus transpulmonary pressure. Kyogoku et al. [6] exploited the availability of central venous pressure in acutely ill children to investigate the possibility of using breath-induced fluctuations in central venous pressure as a surrogate for changes in pleural pressure. Recognizing that the fluctuations in pleural pressure and central venous pressure are not necessarily numerically equal, they took the ingenious step of calibrating one against the other by performing the so-called occlusion test whereby an inspiratory effort is made by the patient when their airway is occluded [8]. The positions and relative swings in pleural pressure and central venous pressure during this maneuver then provide the calibration factors by which central venous pressure is converted into pleural pressure. They compared their central venous pressure-derived estimates of pleural pressure against directly measured changes in esophageal pressure and obtained a good correlation ($R^2 = 0.90$), suggesting that the approach may be useful for estimating pleural pressure and thus transpulmonary pressure. This does not, of course, represent every clinical situation in which transpulmonary pressure might be needed, but in severely ill patients with central venous catheters in place, it may avoid the need to place an esophageal balloon.

In another study related to the monitoring of lung mechanics, Wu et al. [9] also used esophageal pressure along with other variables to optimize mechanical ventilation in a pig model of acute lung injury. This is an area of active research because of the prevalence of acute respiratory distress syndrome (ARDS), which has been recently exacerbated by the SARS-CoV-2 pandemic, and the fact that ARDS can only be managed with supportive care centered on mechanical ventilation [10]. At the same time, mechanical ventilation itself poses a danger to patients because of its potential to cause ventilator-induced lung injury that can make a bad situation worse [11]. Two of the key mechanisms giving rise
to ventilator-induced lung injury are: (1) overdistension of the lung tissues that occurs when part of the lung becomes collapsed so that the entire tidal volume must be forced into the remaining open portion, and (2) repetitive re-opening of closed lung regions that close with each expiration. These two processes give rise to specific types of tissue injury known as volutrauma and atelectrauma, respectively. Wu et al. [9] employed the low-tidal volume strategy [12] that is now standard of care for ARDS patients and is designed to reduce volutrauma. Positive end-expiratory pressure (PEEP) determines how much the lungs can deflate at the end of expiration, and its application reduces atelectrauma, but there is as yet no consensus on how to set the PEEP level. These investigators compared two approaches for setting PEEP: (1) that which maximizes oxygenation, and (2) that which minimizes lung compliance. Both approaches improved the clinical picture, but using transpulmonary pressure to guide the setting of PEEP resulted in less pulmonary edema, lower inflammatory cytokine levels, and reduced lung injured scores compared to setting PEEP on the basis of oxygenation. The next step is probably to compare these approaches in a human clinical trial, although clinical trials in ARDS have a disappointing history of being inconclusive [13–16]. Nevertheless, there is widespread conviction that mechanical ventilation strategies for this dire condition have room for improvement, and pre-clinical studies like this one are a necessary prequel to finding what works in the clinic.

4 Monitoring to guide PEEP settings during surgery

The potential for mechanical ventilation to damage the lungs is present even during routine surgery, where again the need to set PEEP correctly is a prime consideration for the anesthesiologist. And as in the case of ARDS, oxygenation and lung compliance are key parameters that bear on the efficacy and safety of mechanical ventilation during surgery. Ruszkai et al. [17] titrated PEEP by finding the patient-specific values that maximized lung compliance when PEEP was decremented in small steps from 14 cmH₂O. The optimum PEEP levels, which ranged from 8 to 14 cmH₂O, were pitted against a fixed level of 6 cmH₂O in 39 patients receiving cystectomy. Interestingly, although the PEEP-titrated group exhibited improved gas exchange and lung mechanics, there were no significant differences in the rates of post-operative complications. This may reflect the fact that patients with normal lungs are not at risk for ventilator-induced lung injury, and therefore more forgiving of sub-optimal ventilation strategies, compared to patients with ARDS. Nevertheless, the better physiologic picture in the PEEP-titrated group suggests that ventilating so as to avoid ventilator-induced lung injury even in normal lungs may be a good idea and may avoid poorer long-term outcomes, although this remains to be investigated.

In a more nuanced approach to setting optimal PEEP during ventilation of only one lung while monitoring lung mechanics and oxygenation, Spadaro et al. [18] investigated whether it is better to titrate by increasing PEEP incrementally from a pressure of zero up to 16 cmH₂O, or by decreasing it decrementally from 16 cmH₂O after recruiting the lungs with a deep inflation. Both approaches proved beneficial, but only the decremental titration strategy improved oxygenation and reduced the swings in airway pressure needed to ventilate the lungs. These findings fit with the well-known notion in management of ARDS of opening the lungs and keeping them open [19], a rationale which continues to drive studies on mechanical ventilation management [20]. It is achieved by first applying a deep and sustained inspiration to recruit closed lung regions and then immediately applying an appropriate level of PEEP to prevent the lungs from derecruiting again. Also, the pressure required to recruit a closed region of the lung is typically greater than the pressure at which it will derecruit [21], which probably explains the reduced pressure swings observed following the decremental PEEP trial. This study thus further demonstrates the benefits of taking monitoring and ventilation concepts initially developed for critically ill patients in the intensive care unit and applying them to mechanically ventilated patients during surgery [22].

The benefits of recruiting the lung and then setting PEEP via a decremental trial were further investigated by Tusman et al. [23] in the challenging situation of mechanically ventilating severely obese patients in whom the excessive mass of the chest wall and abdomen can apply abnormally high compressive forces to the lungs [22]. These investigators used a multi-modal monitoring approach in which they tracked lung mechanics (with the aid of an esophageal balloon), oxygenation, and total lung gas volumes. Interestingly, they found that the closing pressure of the lung (the pressure at which there is a sudden transition from open to closed units as lung volume decreases) was most accurately identified by oxygen saturation measured by pulse oximetry, which is a completely noninvasive and unobtrusive methodology that is routinely employed during surgery. This provides a convenient way to decide what PEEP level should be applied to obese patients, something that can be a challenge since this level may be very different to the PEEP level that suffices for normal weight patients [22].
5 Detection of patient-ventilator asynchrony

Assessing the characteristics of spontaneous breathing remains one of the most challenging fields in intensive care technology yet is assuming an increasing importance in respiratory monitoring, matching the increased use of assisted modalities of ventilation. In particular, inadequate and asynchronous spontaneous breathing has the potential to aggravate lung injury [24]. Nevertheless, asynchronies can be difficult to assess because they often exhibit complex morphologies during different assisted modes of ventilation. The clinical necessity for minimizing respiratory asynchronies is also not always clear. Recognizing asynchronies, and knowing when to intervene, thus require significant training and skill [25].

Ineffective triggering, which occurs when inspiratory efforts fail to trigger ventilator-assisted breaths [24, 26], was studied by Phan et al. [27] who compared the performance of visual waveform assessment by clinicians against an automated waveform analysis system in detecting ineffective triggering. These investigators used as a reference the information deriving from the electrical activity of the diaphragm as well as oesophageal and transdiaphragmatic pressures. They demonstrated that the ineffective triggering detected by the automated method, which is based only on signals sampled at the airway opening, was in agreement with the reference method that used invasively measured patient effort waveforms. In contrast, the clinicians had a significantly lower sensitivity and only a moderate agreement with the invasively detected ineffective efforts.

The heterogeneous morphology of the spontaneous breathing pattern led Casagrande et al. [28] to apply a machine-learning method to assess the presence of ineffective efforts during expiration. From 8 mechanically ventilated patients they sampled 1500 breaths of which 500 were used for algorithm training and the remaining 1000 for testing. These breaths were classified by three experts as being normal, containing artifacts, or containing different types of asynchronies. The expert classifications and the outputs of the machine learning method were in close agreement, exhibiting a Cohen’s kappa coefficient of 0.983.

Another pressing issue concerning patient-ventilator interactions is the identification of reverse triggering, defined as the condition where the respiratory rhythm is phase-locked to the extrinsic rhythm of the mechanical ventilator [29, 30]. As with ineffective triggering, it is often difficult to identify reverse triggering at the bedside [25], a problem that automatic monitoring tools might help to solve. Rodriguez et al. [31] evaluated an algorithm for detecting double and reverse triggering, both with and without breath stacking, in signals previously recorded from ARDS patients during volume-controlled ventilation. The performance of the algorithm was assessed using two validation breath datasets; the first was adjudicated by an expert from visual inspection of oesophageal pressure tracings in 11 ARDS patients, and the second was adjudicated by vote from a group of 7 experts who evaluated recordings from 99 subjects. These investigators concluded that the automatic algorithm can accurately detect asynchronies related to reverse triggering either with or without breath stacking, although the sensitivity of detection of reverse triggering without breath stacking was slightly lower.

6 Lung ultrasound of diaphragmatic function and in weaning from mechanical ventilation

Until recently, the clinical exploration of lung physiology with methods based on echography has been limited [32] due to a combination of technical issues and lack of familiarity with the method by physicians. However, the last several years have shown a rapid increase in the number of studies focusing upon the development of ultrasonography methods for assessing lung function. In the hands of trained practitioners, ultrasonography can be extremely useful for investigating typical intensive care problems such as pleural effusion, consolidation, pneumothorax, and pulmonary oedema, surpassing the performance of chest X-ray in almost every respect [33].

Ultrasonographic methods are well suited to following diaphragm function [34, 35] during the course of an intensive care or postoperative hospital stay. The increasing use of assisted ventilation modalities has raised awareness of possible diaphragm injuries resulting from spontaneous breathing [30, 34]. Diaphragm dysfunction may also be caused by prolonged disuse or incongruous modalities of mechanical ventilation, even during standard anaesthesia [30]. A typical and frequent problem is the impairment of diaphragmatic function following cardiac surgery, which in turn derives from mechanical or hypothermal damage to the phrenic nerve during the operation. Tralhão et al. [36] compared the bilateral diaphragmatic excursion and thickening fraction seen during spontaneous breathing before and after cardiac surgery, analysing the data from 79 patients, and concluded that immediate post-operative diaphragmatic function is almost always reduced. This dysfunction, however, is transient in the majority of cases and recovers by the 5th post-operative day.

Another important potential application of spontaneous breathing analysis is predicting weaning from mechanical ventilation. This is a particularly important problem in neurosurgical patients in whom, beyond the classical indicators
7 Better Quantifying Ventilation by Electrical Impedance Tomography

Electrical impedance tomography continues to be an emerging topic in intensive care medicine. While local pulmonary ventilation monitoring using electrical impedance tomography is now an established methodology, it also holds the promise of providing local ventilation/perfusion monitoring at the bedside. It remains unclear if this will be based on pulsatile cardiac-related impedance changes or on contrast agent boli passage, or both. In any case, whenever pulsatile impedance is being considered as a signal of interest, a key challenge is the separation of its respiratory versus cardiac-related versus noise components. Separation methods operating in the frequency domain may not be optimal when higher harmonics of the ventilation waveform interfere with the frequency band containing heart activity [41].

As pointed out by Coppadoro et al. [42], proper source-separation filtering in the time domain may avoid this drawback. Assuming ventilation and heart activity to be out of phase, they demonstrate that their “event-triggered average method” can remove cardiac-related impedance changes by averaging the ventilation signal based on a specific triggering point such as the beginning of inspiration. Their algorithm thus has similarities to the method of electrocardiogram (ECG)-gating that peels out the much smaller amplitude cardiac-related signal components from the ventilation-dominated impedance signal [43–45]. These investigators also demonstrate that classical low-pass filtering alters slopes and timing parameters more than their event-triggered algorithm, indicating that higher harmonics of the ventilation signal may get lost by low-pass filtering. However, while the idea of event-triggered averaging is convincing with respect to the reduction of signal distortion, a remaining drawback is that the algorithm cannot be performed in real time.

8 Unobtrusive Respiratory Rate Monitoring at the Edge of Translation to the Bedside

Contact-free monitoring of vital signs is an upcoming field enabling many new medical applications, but also providing increased comfort and ease-of-use for classical cable-bound environments such as the intensive care unit. Over the last few years there has been increasing interest in investigating and comparing all available technologies [46, 47] including capacitive ECG, magnetic impedance, ballistocardiography, radar, and camera-based techniques operating in the visible light frequency range, the near-infrared frequency range, and the far infrared band (Infrared Thermography). As pointed out in the commentary by Marjonivic et al. [48], respiration rate is an often underutilized but nevertheless very important vital sign. They also note there is a need for improved monitoring of respiration rate since this parameter is affected by many common conditions including respiratory failure, metabolic acidosis, renal failure, etc. respiration rate also is key in diagnosing iatrogenic adverse events such as postoperative depression of ventilation by sedative or analgesic drugs.

With a recent decline in price and the parallel increase in performance by orders of magnitude, infrared thermography cameras have followed the development that charge-coupled device cameras exhibited 10 years earlier. However, the big advantage of infrared thermography over charge-coupled device imaging is that infrared thermography cameras can “see” both temperature distribution as well as breathing activity, the latter being detected from temperature changes at the nostrils induced by convective cooling due to air flow. Furthermore, this ability is completely independent of any external illumination, making infrared thermography feasible for ubiquitous round the clock monitoring. In 27 extubated intensive care patients, Chan et al [49] demonstrated that respiration rate monitoring based on infrared thermography agreed with gold standard chest movement counting by two observers (best R = 0.96) and outperformed respiration rate monitoring based on the often-used method of...
ECG-derived bioimpedance. Similarly, in a post-anesthesia recovery unit, Kwon et al.\textsuperscript{[50]} reported that respiration rate monitoring based on infrared thermography in 101 spontaneously breathing patients yielded an $R^2 = 0.9$ between infrared thermography and manual counting based on the clinical monitor. This extends earlier work by Hoehausen et al.\textsuperscript{[51]} who reported an accuracy ($r = 0.607$) of infrared thermography respiration rate monitoring compared to respiration rate derived from ECG-based bioimpedance in 28 postoperative patients. These studies\textsuperscript{[49–51]} collectively demonstrate the increasing sophistication and robustness of respiration rate monitoring algorithms based on infrared thermography as well as the growing use experience of this technology, and can thus be considered important steps on the transition from initial proof of concept studies in adults\textsuperscript{[52, 53]} and infants\textsuperscript{[54]} to clinical practice.

9 Applications of pulse oximetry peripheral perfusion index

Pulse oximetry is a widely applied technology for continuous noninvasive monitoring of peripheral blood oxygen saturation and heart rate. Some pulse oximeters also offer the parameter known as peripheral perfusion index given by the ratio between the pulsatile and non-pulsatile components of the light received by the light-sensitive cell of the pulse oximeter. Changes in the pulsatile component are presumed to reflect changes in pulsatile arterial blood flow, which is the only blood flow component affected by vasoconstriction and vasodilatation \textsuperscript{[55]}.

Prediction of weaning success and detection of failure to wean from mechanical ventilation are important clinical problems, since weaning attempts that are both too aggressive and conservative have been associated with poor outcomes \textsuperscript{[56]}. Readiness for liberation from mechanical ventilation is commonly evaluated by performing a spontaneous breathing trial, which consists of a period with reduced or no ventilator support to determine if a patient can cope with breathing on their own. This is a stressful event for the patient that imposes increased demands for oxygen delivery. Lotfy et al.\textsuperscript{[57]} reasoned that peripheral perfusion index would detect whether or not a patient has the ability to increase cardiac output sufficiently in response to the increased metabolic demands of a spontaneous breathing trial. This is an interesting alternative to the well-studied rapid shallow breathing index, which focuses entirely on the ventilatory response to an spontaneous breathing trial by relating respiratory rate to tidal volume \textsuperscript{[56, 58]}. Eighteen patients out of a group of 43 were considered as weaning failures by Lotfy et al.\textsuperscript{[57]} due to either failing the spontaneous breathing trial (n = 7) or passing the spontaneous breathing trial but requiring reintubation within 48 h (n = 11). Failure of a spontaneous breathing trial was determined according to the standard criteria that consider responses in respiratory rate, oxygenation, heart rate and blood pressure as well as clinical evaluation of respiratory effort and distress. While rapid shallow breathing index measured at spontaneous breathing trial baseline performed better than peripheral perfusion index at baseline in predicting weaning failure and re-intubation, the peripheral perfusion index ratio between baseline and at end of spontaneous breathing trial performed better regardless of timing of rapid shallow breathing index measurement, with sensitivity and specificity of 94% and 72% for predicting weaning failure and 91% and 72% for predicting reintubation, respectively. While not directly comparable, these results compare favorably to the sensitivity and specificity for prediction of successful extubation reported using rapid shallow breathing index in a recent meta-analysis \textsuperscript{[56]}. That ratios of peripheral perfusion index performed better than single index measurements is not surprising since the peripheral perfusion index is known to be heavily skewed and to exhibit significant inter-subject variability \textsuperscript{[55]}. Lotfy et al.\textsuperscript{[57]} reported that the peripheral perfusion index ratio was significantly lower in failed as compared to successful spontaneous breathing trials within 15 min from the start of spontaneous breathing trial, showing an increasing trend in patients who passed the test. This indicates a possible role of peripheral perfusion index in the early detection of poor responses to spontaneous breathing trials, which would allow timely intervention and thus help to avoid the deleterious effect of pushing the patient ‘over the edge’. As these investigators also pointed out, it will be interesting to see if their results in postoperative emergency patients and trauma patients can be extended to other patient groups.

Pulse oximetry is used for continuous monitoring of oxygenation in several circumstances where hypoxic events are likely and timely action is required, such as during surgery, in the emergency department and in the intensive care unit. However, it is well established that oxygen saturation by pulse oximetry should not be considered a replacement for the reference technique of arterial blood-gas analysis. Several studies have investigated agreement between pulse oximetry and arterial blood gas measurements of arterial oxygen saturation showing mean errors in pulse oximetry of 3–4\% \textsuperscript{[59]}. As pulse oximetry accuracy is reduced in low perfusion states \textsuperscript{[60]}, a low peripheral perfusion index value might indicate a poor pulse oximetry signal, thereby suggesting when the more accurate but invasive arterial blood-gas analysis is necessary. This was investigated by Thijsse et al.\textsuperscript{[61]} who compared pulse oximetry and blood-gas saturation in a varied group of 281 intensive care patients. In a total of 1281 measurement pairs, they found a small
pulmonary perfusion index was a poor surrogate for signal quality with a weak correlation between peripheral perfusion index and pulse oximetry to blood-gas difference ($r = -0.17$) and differences $>4\%$ even at peripheral perfusion index greater than 2.5 [61]. They suggest several possible factors that may explain the observed weak association between peripheral perfusion index and measurement inaccuracy, including acid-base disturbances and their effects on local perfusion as well as the oxygen dissociation curve, hemodynamic instability, and use of inotropes. Other possible causes for discrepancy between pulse oximetry and blood-gas analysis include skin pigmentation [62] and oxygen saturation lower than 80% [63]. As also pointed out by Thijssen et al. [61], their findings therefore further support the need for arterial blood gas analysis when accurate measurement of arterial blood oxygen saturation is required. Thus, while peripheral perfusion index did not appear to be a good surrogate for signal quality, it is nevertheless a readily available measurement that could have a role as part of a multifactorial signal quality detection strategy.

### 10 Conclusions

This review provides a summary of selected papers published in the JCMC in the period of 2020-21, highlighting what is new within the area of respiratory monitoring. This is an important topic for JCMC, and the papers reviewed herein demonstrate the breadth and significance of respiratory monitoring within the clinical focus areas of the JCMC. The methods and technologies covered in this review are at varied stages of development, ranging from investigation of early prototypes to use in clinical trials. We expect that these methods, and others within the field of respiratory monitoring, will continue to be refined and extended into novel application areas that advance the practice of clinical monitoring in surgical and intensive care patients.

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