CHEST Recent Advances in Chest Medicine

ICU-Acquired Weakness*

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Observational studies of patients receiving prolonged mechanical ventilation and other forms of critical care support have determined acquired neuromuscular disorders to be extremely common. Early studies used electrophysiologic investigations to diagnose critical illness polyneuropathy (CIP) and muscle biopsy to confirm critical illness myopathy (CIM). More recent approaches seek to obviate these invasive techniques and build on a standardized bedside neuromuscular examination to identify patients with acquired weakness syndromes. Serial examination in the alert patient may serve as a reasonable prognosticator for most patients.
The importance of ICU-acquired weakness syndromes is supported by the observation that muscle wasting and weakness are among the most prominent long-term complications of survivors of ARDS. In addition, a strong association appears to exist between acquired weakness and protracted ventilator dependence, an important determinant of ICU length of stay. Multivariate analysis has identified several risk factors associated with increased incidence for ICU-acquired weakness, including severe systemic inflammation, medications (specifically, corticosteroids and neuromuscular blocking agents), glycemic control, and immobility. We advocate an approach to this common syndrome that identifies risk factors early in the hope of minimizing their impact. ***(CHEST 2007; 131:1541–1549)***

Key words: critical illness; ICU-acquired weakness; myopathy; polyneuromyopathy

Abbreviations: CIM = critical illness myopathy; CIP = critical illness polyneuropathy; CMAP = compound muscle action potential; ICU-AP = ICU-associated paresis; ICU-AW = ICU-associated weakness; MRC = Medical Research Council; NMBA = neuromuscular blocking agent

Wasting syndromes associated with protracted infection have long been recognized. Osler[1] commented on the "rapid loss of flesh" observed in patients with prolonged sepsis in the preantibiotic era. With the advent of improved cardiopulmonary support for the critically ill, syndromes of pronounced neuropathy and myopathy are increasingly recognized in the survivors of acute critical illness.

Investigations of patients with prolonged sepsis and severe motor dysfunction recognized during convalescence first appeared in the 1980s.[2] Over the next 25 years, comprehensive evaluations for these disorders have supported the significance of these initial investigations. Electrophysiologic testing, histopathologic evaluation, and prospective cohort studies[3–14] have created a substantial body of literature on neuromuscular disease in critical illness that highlights common risk factors and delineates the extent of injury.

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Variation in terminology and nosology characterizes this literature. Disease states, such as critical illness polyneuropathy (CIP) and critical illness myopathy (CIM), have been defined by advanced neuromuscular testing and muscle biopsy that are not uniformly performed in routine critical care. Given the dichotomy between the commonality of weakness in the critically ill and the limited number of electrophysiology tests performed, this review embraces an overarching term for neuromuscular disease in the critically ill: *ICU-acquired weakness*

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(ICU-AW). This diagnosis, defined simply by structured examination, can be applied more generously and may permit more uniform reporting of affected patients by intensivists. Case definitions for each neuromuscular disease state will be clarified below.

Clinical Presentation

Patients with ICU-AW are usually recognized in two bedside contexts. Most commonly, the clinician struggling to liberate a patient from mechanical ventilation will entertain the diagnosis of weakness. This diagnostic evaluation focuses initially on the respiratory muscles. The patient with ICU-AW, while slowly and globally recovering, exhibits generalized weakness that impairs not only return to spontaneous breathing but mobilization in general. The second bedside context involves the patient with such profound weakness despite return of sensorium that causes of quadriplegia are entertained. In both cases, if neuromuscular function recovers, it often lags well behind other organ system repair.

Physical examination of patients for ICU-AW is dependent on the cooperation and maximal effort of the patient, an aspect of bedside assessment that can be confounded by sedation, delirium, encephalopathy, and other ICU influences on cortical brain function. When a reliable motor examination is possible, affected patients will exhibit generally symmetrical motor deficits in all limbs, ranging from paresis to true quadriplegia.[15] A standardized bedside muscle examination can be utilized to evaluate individual muscle groups. The Medical Research Council (MRC) score includes formal testing of three muscle groups in each limb on a scale from one to five (Table 1).[16] This scoring has demonstrated excellent interrater reliability, including evaluations of patients with Guillain-Barre syndrome receiving mechanical ventilation,[17] and can be utilized to document the extent of disease and track serial changes over time (assuming intact cognition).

An early clue that may be noted by care providers is that painful stimulation (such as pressure on the nail bed) results in a limited to absent limb response, yet normal grimacing. This finding highlights the usual sparing of weakness in the facial muscles. Limited information is gleaned from the assessment of reflexes and the sensory examination. Reflexes are usually diminished or absent, but normal reflexes do not rule out the diagnosis. Sensory examination is often curtailed by patient sensorium, interaction with the examiner, and edema.

Once a weakness syndrome is entertained, the clinician must clearly establish the absence of a neuromuscular condition that began before admission to the ICU. Careful review of the premorbid functional status must be undertaken. Usually a determination of the performance of activities of daily living and ambulation suffices. Acute spinal cord injury, motor neuron disease, Guillain-Barre syndrome, myasthenia gravis, Lambert-Eaton syndrome, and muscular dystrophy are usually evident prior to the initiation of mechanical ventilation. However, these conditions may rarely emerge during critical illness and, in selected patients, neurologic assessment must be undertaken for these entities.[18]

Table 1—*MRC Scale for Muscle Examination

Functions assessed
Upper extremity: wrist flexion, forearm flexion, shoulder abduction
Lower extremity: ankle dorsiflexion, knee extension, hip flexion
Score for each movement
0–No visible contraction
1–Visible muscle contraction, but no limb movement
2–Active movement, but not against gravity
3–Active movement against gravity
4–Active movement against gravity and resistance
5–Active movement against full resistance
Maximum score: 60 (four limbs, maximum of 15 points per limb) [normal]
Minimum score: 0 (quadriplegia)

*Adapted with permission from Kleyweg et al.[16]

Distinction Between Polyneuropathy and Myopathy

Since delirium and sedation are frequent in ICU patients, reliable bedside examination of neuromuscular function can be difficult. Given these obstacles, (early) studies of seemingly weak patients have relied on electrophysiologic testing to provide a rigorous description of underlying neuromuscular dysfunction. Comprehensive electrophysiologic studies including motor and sensory nerve conduction studies as well as needle electromyography in the upper and lower limbs defined two broad categories of ICU-AW: CIP and CIM. Brief introductions to each entity will be described below; comprehensive reviews[7,18–20] of these entities are available.

In CIP, electrophysiologic testing usually shows sensorimotor axonopathy with decreased compound muscle action potential (CMAP) and sensory nerve action potential yet normal nerve conduction velocities (assuming the absence of persistent neuromuscular blockade).[18] Abnormalities may be detected as early as 48 h into critical illness.[21] Spontaneous muscle activity with fibrillation potentials can be detected in severe axonal disease.

An accompanying prolongation of the CMAP du-

ration suggests an associated myopathy.[7] CIM is an acute primary myopathy (not secondary to muscle denervation) and is diagnosed by abnormalities of the electromyographic tracing during a voluntary contraction (requiring patient cooperation). Affected muscle exhibits a characteristic pattern of abundant low-amplitude, short-duration polyphasic units with early recruitment.

The definitive diagnosis of muscle involvement requires examination of muscle tissue by biopsy. The reported light-microscopic findings in specimens from CIM patients include muscle fiber atrophy (preferentially type II fibers), occasional fiber necrosis, regeneration, and decreased or absent reactivity in myofibrillar adenosine triphosphatase staining, corresponding to a selective loss of myosin filaments. This selective loss of myosin is practically pathognomonic for CIM. To minimize the morbidity of an open muscle biopsy, some[22] have proposed quantification of myosin/actin ratio by gel electrophoresis in core needle specimens (conchotome muscle biopsy technique) to diagnose CIM.

To overcome the challenges of patient cooperation and completely avoid muscle biopsy, the method of direct muscle stimulation has been evaluated. First proposed by Rich et al[23,24] in 1996, direct muscle stimulation was intended to differentiate between CIM and CIP. Both conditions demonstrate reduced nerve-evoked CMAP amplitude, yet denervated muscle (as in CIP) should retain electrical excitability and the direct muscle stimulation CMAP amplitude should be normal. CIM patients should exhibit loss of electrical excitability, and both nerve- and direct muscle-stimulated CMAPs should be diminished. Several groups have since studied this modality, but analysis has been troubled by the common overlap of CIM and CIP[25] or the absence of muscle biopsy correlates.[26]

As further series of patients were described,[27] significant overlap of CIP and CIM was noted, leading to the use of a new descriptive term *critical illness polyneuromyopathy* (CIPNM, also known as *CIM and/or neuropathy*). Several investigators[14,27] have demonstrated that when sought, myopathy is often present in conjunction with the established evidence for neuropathy. For example, Latronico et al[27] demonstrated that 19 of 24 patients with CIP had evidence of myopathy when muscle biopsy was performed.

As critical care practice has evolved to a "least sedation" model, the ability to evaluate patients with a comprehensive bedside examination has become more feasible, perhaps making extensive electrophysiologic testing less necessary. De Jonghe and colleagues[10] prospectively evaluated 95 patients who had received mechanical ventilation for $>$ 7 days and achieved satisfactory awakenings for MRC examination. Patients with a score of $<$ 48 were delineated to have ICU-acquired paresis (ICU-AP). All patients with ICU-AP demonstrated sensory motor axonopathy, and histologic features of primary myopathic changes were observed in all patients with paresis 1 week after the initial diagnosis. This term is essentially synonymous with the term used broadly in North America: *ICU-AW*.

These authors[10,15] have advocated using physical examination as the primary determinant of ICU-AW. Patients demonstrating the characteristic examination combined with any evidence of recovery on serial examination usually require no further investigation. Patients with a protracted altered sensorium or fixed motor deficit should undergo further testing for CNS pathology.

Controversy Regarding Neuromuscular Investigations

The decision to perform electrophysiologic testing and/or muscle biopsy in routine care, as opposed to research settings, has created an ongoing debate in the medical literature. Proponents[27] cite evidence that clinicians have predicted fatal outcomes in acutely ill, comatose patients with paralysis developing despite neurologic signs and physiologic and radiologic investigations that do not indicate irreversible brain damage. Coma, a potent predictor of mortality and morbidity in critical illness, coupled with the absence of movement, is commonly considered a "deadly sign."[19,28] However, patients with CIP and CIM, potentially reversible entities, should be carefully identified to avoid unreasonably pessimistic prognoses. Predicted outcome has been shown to alter patient treatment[29]; therefore, accurate predictions are paramount in decisions regarding goals of care in the patient with protracted critical illness.

Advocates for routine clinical examination who reserve neurophysiologic testing and biopsy for unusual or severe instances of weakness cite the limitations, costs, and risks of this testing. Edema, artifacts related to the presence of multiple electrical devices, and invasive catheters are common sources of technical difficulties with electrophysiologic testing in ICU patients.[30] In addition, neurophysiologic testing does not predict duration of mechanical ventilation nor ICU stay, and the presence of CIP and/or CIM does not ensure reversibility.[31] Importantly, there is not a specific therapy for CIP and/or CIM; therefore, establishing a highly specific or physiologically based diagnosis does not translate to a specific pharmacologic therapy. Rather, therapies currently employed to limit ICU-acquired weakness

are preemptive and should be applied to virtually all critically ill patients receiving mechanical ventilation (see discussion following).[31]

Additional practical factors may influence the decision to perform these tests. Neuromuscular specialists with expertise in electrophysiologic testing and biopsy interpretation are in limited supply, while critically ill patients undergoing mechanical ventilation are ubiquitous. In addition, the continuity of care enjoyed by intensivists is far different than the consultative role of a neuromuscular specialist. Intensivists have the opportunity to serially evaluate a patient's neuromuscular and psychological state over time, including subtle changes in performance (particularly when sedation limitations are implemented appropriately). Neuromuscular specialists are often requested for consultation during the latter stages of critical illness and asked to diagnose and prognosticate in a finite capsule of time. It is not surprising that advanced diagnostic tools would then be utilized to create a prompt and comprehensive response.

Proposed Diagnostic Algorithm

To optimize the likelihood of patient interaction for neuromuscular assessments, we advocate the implementation of sedation protocols.[32,33] Our preference, daily interruption of sedative infusions, confers the opportunity for serial neuromuscular examination and reduces the duration of mechanical ventilation.[32,34] Careful implementation of the structured MRC examination should be employed and documented serially as a matter of routine. Patients exhibiting fixed or focal motor defects or persistent altered sensorium despite adequate sedation washout should undergo more advanced diagnostics (*ie*, CNS imaging, electrophysiologic studies, and/or muscle biopsy) [Fig 1].

Epidemiology

The occurrence of ICU-acquired weakness varies substantially depending on the patient case mix, diagnostic method used, and the timing of examination. De Jonghe et al[10] found clinically significant ICU-AW in 25% of patients who received mechanical ventilation for at least 7 days. Of note, a substantial number of patients could not be evaluated by muscle strength testing, most commonly the result of death before regaining consciousness. Electrophysiologic testing to delineate CIP does not share similar limitations in the unresponsive patient, and has resulted in reports of higher incidences of acquired neuromuscular disease in similar cohorts. For exam-

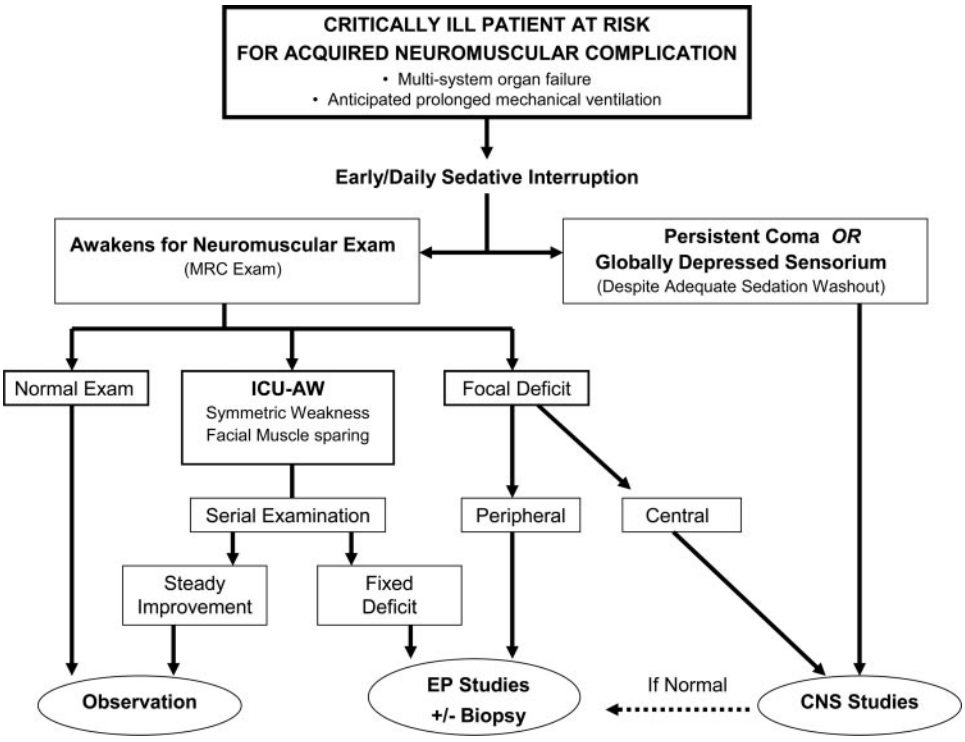

Figure 1. Proposed diagnostic algorithm for assessing neuromuscular complications in the critically ill. EP = electrophysiology; +/− = with/without.

ple, a prospective study[35] of 50 patients receiving mechanical ventilation for > 7 days documented CIP in 58%. Studies[8,36,37] using cohorts restricted to sepsis and multiorgan failure have found even higher incidences of neuromuscular disease, ranging from 50 to 100%.

Outcomes

Understanding the evolving terminology described above is important when reviewing outcome studies of these patients. The combination of varied definitions of neuromuscular impairment and selected cohort analysis creates the risk of bias and makes comparisons across studies challenging. Even with these limitations, ICU-AW appears to have a significant association with short and long-term measures of outcome.

Short-term Outcomes

Two studies[38,39] have demonstrated that weakness is an independent predictor of prolonged mechanical ventilation. Garnacho-Montero and colleagues[38] evaluated septic patients receiving ventilation for at least 7 days for CIP. Patients with electrophysiologic evidence of CIP had longer duration of mechanical ventilation than patients who did not (median, 34 days vs 14 days; $p < 0.001$). This finding was explained by a longer period required for weaning and was associated with an increased length of ICU and hospital stay. De Jonghe and colleagues[39] evaluated ICU patients receiving ventilation for at least 7 days who were sufficiently awake to permit evaluation for ICU-AP. Of the 95 patients enrolled, 24 patients (25%) had ICU-AP. The weak patients exhibited a similarly increased period of weaning and duration of mechanical ventilation as compared to the nonweak cohort. In the multivariate analysis incorporating severity of illness scoring, disease states, and duration of multiple organ dysfunction, the two independent predictors of prolonged weaning, were ICU-AP (hazard ratio, 2.4) and COPD (hazard ratio, 2.7). [39]

Two studies[35,40] have demonstrated increased mortality in patients with CIP. Garnacho-Montero et al[40] studied a very select population of severely ill patients: septic patients with multiple organ dysfunction syndrome requiring mechanical ventilation for > 10 days. Patients with CIP had higher in-hospital mortality rates than those without CIP (84% vs 56.5%, $p = 0.01$). Similarly, Leijten et al[35] found that in 50 patients receiving mechanical ventilation for > 7 days, ICU mortality was higher in the CIP group (48% vs 19%, $p = 0.03$).

Despite the demonstrated associations between ICU-AW and poor short-term outcomes, there is no clear cause-and-effect relationship. Attempts have been made to statistically adjust for imbalances between weak and nonweak cohorts,[39] yet no conclusive evidence exists to refute the possibility that poor outcomes and weakness may simply reflect the type and/or severity of the patient's underlying condition.

Long-term Outcomes

Muscle wasting and weakness are common and often striking in survivors of critical illness. In a comprehensive evaluation of a cohort of 100 survivors of ARDS, patients were evaluated at 3, 6, and 12 months following critical illness via physical examination, pulmonary function testing, 6-min walk testing, and quality of life evaluation.[41] Extrapulmonary conditions, specifically muscle wasting and weakness, were the most prominent complications and were responsible for much of the persistent functional disability. Retrospective data[42] suggest that in high-risk groups such as patients with ARDS, CIP and/or CIM may be present in as many as 60% of patients.

Latronico and colleagues[43] made a composite evaluation of studies reporting long-term outcomes in patients with CIP and CIM. Inclusion of 36 studies provided information on the outcomes of 263 patients. Mean duration of follow-up was 3 to 6 months (range, 2 days to 8 years). Complete functional recovery with patients regaining the ability to breathe spontaneously and to walk independently was reported in 68% (180 of 263 patients). Severe disability with quadriparesis, quadriplegia, or paraplegia was reported in 28% (74 of 263 patients). Persisting milder disabilities were common even in patients with complete functional recovery, and included reduced or absent deep tendon reflexes, stocking and glove sensory loss, muscle atrophy, painful hyperesthesia, and foot drop.[44]

Risk Factors

Factors such as systemic inflammation, medications, electrolyte disturbances, and immobility have been implicated in the pathogenesis of ICU-AW. In the absence of an experimental model to explore mechanisms of injury, current information derives largely from prospective cohort studies of patients utilizing multivariate analyses to assess independent risk factors.

Systemic Inflammation

Pioneers in the field of neuromuscular disease in the critically ill recognized the correlation of ac-

quired weakness with the systemic inflammatory response syndrome, sepsis, and multisystem organ dysfunction.[4,8,45,46] Two prospective studies[9,10] have further validated the relationship to inflammation. de Letter et al,[9] coupling clinical examination and electrophysiology, demonstrated that acute physiology and chronic health evaluation (APACHE) III scores and the presence of systemic inflammatory response syndrome were independently associated with the development of CIPNM. Based on the distribution of the predictive index of these two variables, three risk groups were determined to assist in risk stratification for the development of CIPNM. This model has yet to be tested prospectively. De Jonghe et al[10] demonstrated that prolonged multisystem organ failure is strongly associated with the development of ICU-AP. How systemic inflammation would produce nerve and muscle injury is unclear; commonly invoked pathways include ischemia or injury via mediators of inflammation. de Letter et al[47] have additionally demonstrated evidence for low-level, local immune system activation with release of both proinflammatory and antiinflammatory cytokines in the muscle of patients with critical illness polyneuromyopathy. Tissue injury may lead to the influx of inflammatory cells and the release of such cytokines. The expression of adhesion molecules on vascular endothelium suggests the possible contribution of increased vascular permeability. While these local phenomena may be important, measurement of more global markers of inflammation, such as interleukin-6 and tumor necrosis factor, has not shown them to be elevated in the serum of patients with CIP as compared to nonweak, critically ill control subjects.[48]

Medications

Many medications have been implicated as causes of weakness. Corticosteroids, the most widely studied,[10,41,49] have a significant association with the development of ICU-AW. In animal models, administration of corticosteroids can produce selective muscle atrophy, particularly of fast-twitch fibers.[50] However, a thick filament myopathy identical to CIM can be best produced by combining denervation injury and corticosteroids.[51] In such an animal model, complete loss of muscle excitability was found, now ascribed to the inactivation of fast sodium channels.[52] This "two-hit" hypothesis has been invoked to explain the profound forms of CIM described in patients with status asthmaticus.

A recent prospective, randomized trial[53] of methylprednisolone for persistent ARDS demonstrated no improvement in 60-day mortality despite evidence for early physiologic improvement of gas exchange and lung mechanics. The small number of patients with significant complications attributed to neuromyopathy were all in the methylprednisolone-treated arm. It is plausible that some benefits of corticosteroid treatment on lung function were offset by the adverse effects on strength.

The association of neuromuscular weakness with prolonged use of neuromuscular blocking agents (NMBAs) has long been recognized and is the most prominent reason for a shift away from NMBA use in the critically ill. An association of NMBA use with CIP has been noted in one study[40] but was absent in others. While the association of NMBAs with CIP remains unclear, there are well described scenarios of ICU-AW with these agents. One scenario is that of prolonged neuromuscular blockade arising from persistent drug effect, such as that occurring with agents (or their metabolites) that accumulate in the setting of renal and liver failure. The second scenario involves patients with severe acute asthma and ventilatory failure who undergo treatment with high-dose corticosteroids in combination with NMBAs. These patients may exhibit severe and protracted myopathy.[54–56]

Glycemic Control

The link between elevated blood glucose levels and ICU-AW was established in an early study[8] of critically ill patients with multisystem organ failure. More recently, a large randomized trial[57] of surgical patients undergoing tight glycemic control with insulin infusions vs conventional insulin therapy demonstrated a 50% reduction in the evolution of CIP. Secondary evaluations of this data set link the protective effect to strict glycemic control as opposed to the insulin effect.[58] The impact of tight glycemic control on preservation of neuromuscular function in medical ICU patients has yet to be described.[59] However, given other proven salutary effects of such management (including reductions in days to weaning of mechanical ventilation, ICU and hospital length of stay, and development of renal injury), we do advocate the application of tight glycemic control in patients receiving mechanical ventilation.

Immobility

Bed rest and deep sedation have been suggested to potentiate ICU-AW. Three pieces of indirect evidence support such speculation. De Jonghe et al[10] found that duration of mechanical ventilation prior to "awakening" to establish the diagnosis of ICU-AP was a significant risk factor, independent of the duration of multiple organ failure. Contributors to alterations in patient sensorium delaying the diagnosis might be causal (*ie*, sedatives). Second, a rabbit

model utilizing controlled mechanical ventilation demonstrated atrophy of the diaphragm within a few days of respiratory-muscle inactivity.[60] Finally, repeated daily passive mobilization has prevented muscle atrophy on serial muscle biopsies in patients receiving mechanical ventilation and NMBAs.[61]

In contrast, Eikermann et al,[62] utilizing electrophysiologic studies and direct muscle stimulation, demonstrated that septic patients with multiple organ failure have reduced muscle force without evidence for increased fatigability. Healthy patients undergoing limb immobilization did not exhibit reductions in force or fatigability. Seemingly, immobilization alone cannot create CIM.

Prevention/Treatment

Data supporting specific approaches to prevent or treat ICU-AW are limited. For the practicing clinician, it is reasonable for ICU-AW to be approached as a syndrome with a large number of potential associations. Akin to the approach to delirium, the causes are multiple and overlapping.[63,64] We advocate that the clinician seek potentially reversible risk factors and adjust care accordingly (Fig 2).[65]

The best evidence for prevention comes from a secondary end point of a trial of strict glycemic control via insulin infusion in critically ill surgical patients. Intensive insulin therapy (maintenance of a blood glucose level from 80 to 110 mg/dL) demonstrated a mortality benefit and fewer cases of CIP detected by routine electrophysiologic testing after day 7 (28.7% vs 51.9%, $p < 0.001$).[57] This management seems appropriate assuming a careful implementation with safeguards against potentially injurious hypoglycemia.[59]

Given the evidence for reduced muscle atrophy with passive limb muscle stretching,[61] strategies to mobilize patients, either with passive stretching or active exercises with physical and occupational therapy, seem reasonable when approached in a safe, systematic manner. At the least, sedation protocols designed to minimize the use of sedatives and analgesics have been shown to decrease duration of mechanical ventilation.[32,66] This strategy may help to promote earlier patient wakefulness, minimize sedative-induced immobility, and permit earlier recognition of weakness with earlier mobilization as tolerated.

Medications that may increase the risk of weakness should undergo careful review. Corticosteroids should be used with caution, if at all, in circumstances in which benefit is obscure, such as late-phase ARDS.[53] Ideally, further investigations will help guide use of corticosteroids in the critically ill, extending the observations already made in patients with severe community-acquired pneumonia[67] and septic shock.[68]

It also seems prudent to maintain the internal milieu of the patient, with attention to electrolyte disorders, including phosphate and magnesium depletion. Although not proven, adequate nutrition supplementation seems a necessity, as the body will otherwise cannibalize muscle for sources of energy.

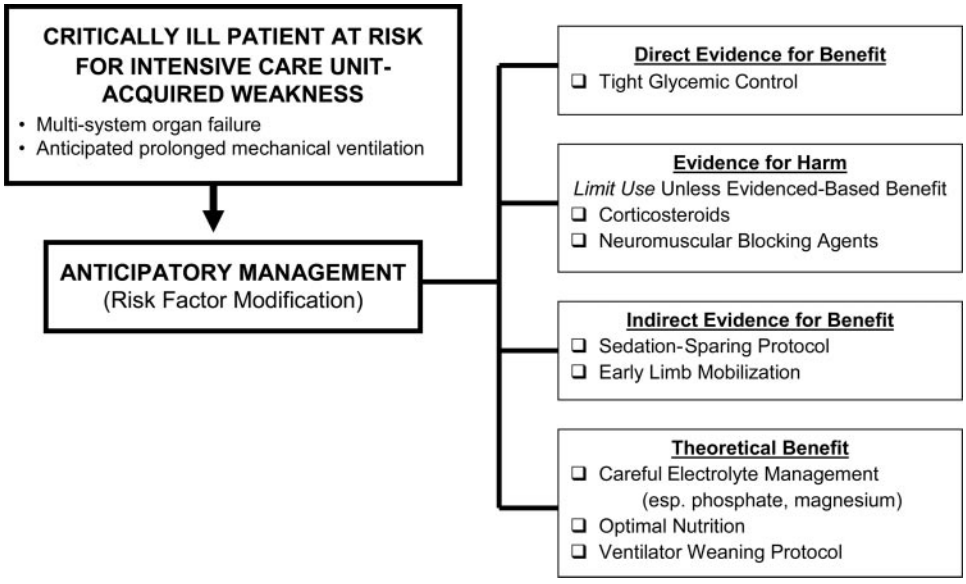

Figure 2. Risk factor modification schema for patients at risk for ICU-acquired weakness. esp = especially.

Finally, standardized approaches to ventilator weaning, such as a respiratory therapist-driven protocol, must be employed to minimize the duration of ventilator dependence.[69]

In contrast to the study-limited approach for clinical care, research mandates a more comprehensive evaluation. Study patients may require the coupling of physical examination with comprehensive electrophysiologic testing and biopsy results. Furthermore, the contribution of the diaphragm must be better understood.

Conclusions

An aging baby boomer population combined with increasing numbers of patients needing and seeking ICU services creates an environment in which critical care delivery must be optimal. Longer-term outcomes focusing on neuromuscular strength and patient functional autonomy need to be considered when evaluating the quality of interventions. Although it seems doubtful that a single therapy might prevent weakness in such varied populations, the meticulous application of a multipronged therapeutic approach including tight glycemic control, optimal nutrition, early limb mobilization, and avoidance of risk factors such as excessive sedation, high-dose steroids, and paralytics may help to ensure maximal functional status for survivors of critical illness.

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ICU-Acquired Weakness*

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Editorials

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Managing the Nervous System Effects of Sepsis

Sepsis and multiple organ failure (critical illness, systemic inflammatory response syndrome) develop in the majority of patients receiving mechanical ventilation for ≥ 1 week in major medical and surgical ICUs, and the majority are nervous system complications of septic encephalopathy,[1,2] critical illness polyneuropathy (CIP),[3] and critical illness myopathy (CIM).[4] These complications appear as stupor or coma, difficulty weaning from mechanical ventilation, and limb weakness. As intensivists struggle to overcome the complex problems of sepsis and multiple organ failure, these nervous system complications are either overlooked or misdiagnosed. Stupor is attributed to sedation, weaning difficulties to diaphragmatic fatigue, and limb weakness to catabolic myopathy. With successful weaning, the patient is discharged to a general ward, where the patient experiences impaired cognition; difficulty dressing, eating, and rising from the bed or toilet seat; difficulty standing and walking; shortness of breath; and fatigue. A prolonged stay in a rehabilitation center may be necessary. Unless further investigated, the nature of these symptoms remains unexplained and a puzzle to the patient, family, and caregivers.

Comprehensive neurologic assessment during ICU stay will identify these nervous system complications.[5] CT head scans and cerebrospinal fluid examination are unremarkable in septic encephalopathy, but the EEG shows abnormalities consistent with a diffuse encephalopathy. Electromyography (EMG) and nerve conduction studies of the limbs, measurement of creatine kinase, and at times muscle biopsy will disclose the presence and severity of CIP, CIM or, as is often the case, a combination of both conditions. The knowledge gained will aid management: determining the need and type of sedation, adjustments in weaning procedures tailored to neuromuscular respiratory insufficiency, and early rehabilitation.

Intensivists are now beginning to realize the importance of these nervous system complications. The "least-sedation" method of briefly discontinuing sedation each day and determining the level of alertness is now used as a guide to managing sedation in some ICUs.[6,7] In this issue of *CHEST* (see page 1541), Schweickert and Hall[8] provide a comprehensive review of what they term *ICU-acquired weakness* (ICU-AW), and they propose that it be assessed in conjunction with the least-sedation method to assess muscle strength. When the patient becomes alert enough, limb strength can be tested through voluntary activation with grading according to the Medical Research Council scale (see Table 1 in Schweickert and Hall[8]). The method has proved reasonably accurate in patients with Guillain-Barré syndrome.[9] In a prospective study by De Jonghe et al,[10] utilization of this method identified 28% of patients who had sepsis and multiple organ failure as having CIP and CIM, demonstrated by subsequent electrophysiologic studies and muscle biopsy. The weak patients had a longer duration of weaning and mechanical ventilation than patients who were not weak.

An early sign of CIP or CIM is observed when testing the level of consciousness in a patient who is stuporous or comatose; nail bed pressure will evoke weak or absent limb movements but obvious facial grimacing. Another early sign is loss of tendon reflexes that were previously present.[5] These early signs could be added to the above protocol. All signs could be readily taught to ICU nurses.

Schweickert and Hall[8] propose that once ICU-AW is identified, if there is improvement, no further studies are needed. However, if there is deterioration, further nervous system tests including CT head scan, electrophysiologic studies (EEG, EMG), and possibly muscle biopsy are performed. Earlier identification of the problem, noting its course, possibly its exact nature, may aid further management: problems with sedation, the use of neuromuscular blocking agents and steroids (which are thought to predispose to CIM), and early rehabilitation.

This proposal is welcome, and we recommend it be adopted in all major medical and surgical ICUs. It must however be realized that only a quarter of those with CIP and CIM would be identified by clinical examination alone. A further quarter or more would be identified by electrophysiologic studies. Not only do

electrophysiologic studies help establish the diagnosis of CIP and CIM, they are invaluable in eliminating other conditions. For example, myasthenia gravis, Lambert-Eaton myasthenic syndrome, and amyotrophic lateral sclerosis may present, for the first time, as acute respiratory insufficiency requiring mechanical ventilation and admission to an ICU.[5] Thus, patients with long-term neuromuscular disability and those "stuck on a ventilator" who are managed in chronic care respiratory facilities remain undiagnosed.

In the future, electrophysiologic monitoring may become feasible. For example, EEG monitoring would disclose the varying effects of sedation, septic encephalopathy, or the combination of both.[11] The simple measurement of the compound muscle action potential of the thenar muscle by stimulation of the median nerve at the wrist would detect a drop in amplitude as an early sign of CIP and CIM.[5] Park et al[12] have shown that an increase in the duration of the compound muscle action potential in addition to the drop in amplitude is specific for CIM. For research purposes, these methods would be sensitive to changes induced by interventions designed to alleviate sepsis and its nervous system complications.

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Statins and Lung Cancer Risk

Lung cancer is the second-most-common cancer diagnosis in men and women.[1] It accounts for more deaths than prostate, breast, and colon cancer combined. Many risk factors for lung cancer have been identified. Smoking is the most prominent and modifiable risk factor. Still, 10 to 15% of lung cancers occur in those who are lifetime neversmokers (a person who has smoked < 100 cigarettes during lifetime) and 55 to 65% in those that have quit smoking. Many treatment modalities including chemotherapy, radiation, and surgery are now available for lung cancer therapy; however, the survival rates for the 60 to 70% of patients who present with advanced disease remain dismal.

To reduce the incidence of lung cancer, focus has turned to chemoprevention: the use of agents to reduce, prevent, or reverse carcinogenesis.[2] Agents explored to date have been ineffective, and in the case of beta-carotene have even shown harmful effects. Multiple *in vitro* and epidemiologic studies had suggested a chemopreventative effect for beta-carotene on lung carcinogenesis. However, once tested under rigorous prospective conditions in randomized phase III trials,[3,4] beta-carotene was associated with an increased lung cancer risk rather than the hypothesized decreased risk. This speaks to the importance of evaluating agents in a randomized prospective fashion as the "gold standard" for proof of efficacy (*ie*, a reduction in cancer incidence).

Statins have become a cornerstone in the treatment of patients with atherosclerotic disease, since their use has resulted in improvements in outcome. In addition to their lipid-lowering effects through inhibition of hydroxy-methylglutaryl coenzyme A reductase, statins have antitumor effects *in vitro*. They have been demonstrated to increase apoptosis,[5] suppress angiogenesis through their effects on vascular endothelial growth factor,[6] and alter invasion

and metastatic potential through interaction with adhesion molecules.[6] In addition, epidemiologic data have shown an association between the use of statins and a decrease in cancer incidence.[7,8]

However, data also exist against the use of statins for the chemoprevention of cancer. To clarify these findings, large metaanalyses have been published. Dale et al[9] published a metaanalysis evaluating 26 randomized controlled trials of statins. They found no beneficial or detrimental effect of statins in relation to overall cancer risk or cancer death, a result echoed by another metaanalysis[10] of 35 randomized controlled trials.

The study by Khurana et al[11] in this issue of *CHEST* (see page 1282) is a retrospective case-control study that evaluated the potential impact of statins on the development of lung cancer in $>$ 400,000 patients seen in Department of Veterans Administration hospitals. Lung cancer was diagnosed in approximately 7,300 of these patients (1.5%), and statin use $>$ 6 months was associated with a 55% reduction in lung cancer risk ($p < 0.01$). This benefit was observed even after controlling for age, history of tobacco use, and race.

These results are encouraging and strengthen the hypothesis that statins may be useful for lung cancer chemoprevention. However, as pointed out by the authors,[11] the study has weaknesses innate to its design. Firstly, it is a retrospective analysis of mainly male veterans, and thus only partially representative of the diverse population of the United States. In particular, the impact of statins on lung cancer risk in women cannot sufficiently be addressed. Secondly, the interaction between tobacco and statin use can only be marginally investigated in the data set because of uncertainties in data accuracy. Other exposures to chemicals, radiation, and potentially carcinogenic substances were not explored in depth. Statins were obviously used in this population for specific clinical indications, thus limiting the observation to patients with specific medical conditions. Finally, aside from the lung cancer risk reduction, patients with a $<$ 6-month use of statins had an increased risk of lung cancer, which raises the question of a potential tumor promoting effect of statins.

Many questions remain regarding the application of statins for chemoprevention of lung cancer. Does the dose of statins play a role in its effect? What about treatment duration? Is one statin superior to another? Perhaps the lung cancer risk reduction in this population is a result of other lifestyle changes, for instance diet and exercise, and not etiologically related to statin use? To answer these and other questions, prospective data need to be obtained in controlled clinical trials, possibly with surrogate biomarkers as the primary end point initially to minimize time, cost, and sample size of such studies. At present, statins should be utilized based on the strict guidelines of the Adult Treatment Panel III[12] until data from randomized controlled phase III trials with lung cancer incidence and/or mortality as primary end point become available.

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Another Nail in Albumin's Coffin

In this issue of *CHEST* (see page 1295),[1] one finds another important investigation that addresses one of the fundamental tenets of acid-base physiology: the role of albumin as a buffer base. Few therapies have entrenched themselves in medicine with the same tenacity as albumin administration. According to conventional wisdom, albumin functions as a buffer base and should, therefore, blunt the acidosis generated by increases in P_{CO_2}. In an elegantly designed investigation, Gomez and colleagues[1] varied P_{CO_2} in rodents with either normal albumin, hypoalbuminemia, or analbuminemia. If albumin serves this central buffer base role, then for a given increase in P_{CO_2}, the effects of acidosis (principally hypotension) should be proportional to the decrement in albumin from normal. Despite identifying a decreased buffer capacity in the hypoalbuminemic and analbuminemic rats, no such BP effect was observed. This observation casts further doubts onto the time-honored practice of albumin administration in the critically ill, as one can no longer support such a practice on the basis of acidosis buffering in the setting of permissive hypercapnia for lung injury or ARDS.[2]

The authors[1] explored nitric oxide (NO) production as a potential explanation for the lack of BP effect in groups with different albumin concentrations. No differences in NO production were identified, with all groups increasing NO production with hypercapnia. While baseline nitrite levels were diminished in rats with decreased albumin, NO production in response to hypercapnia and acidosis increased in these groups to a greater extent than in their normoalbuminemic counterparts. Thus, the data suggest an increased endothelial sensitivity to NO in the presence of decreased buffer capacity and acidosis. Such a mechanism would support mean arterial pressure and organ-based perfusion pressure. This group has a long-standing interest in acid-base physiology based on physicochemical principles[3] and utilized this model to ascertain additional data underlying the mechanism of acid-base homeostasis with abnormal albumin concentrations, modeling the clinical circumstance.

Utilizing the principles of charge balance determining acid-base balance espoused by Peter Stewart in 1983,[4] Gomez et al[1] identified that the normal acid-base balance manifested in each of the groups relied on different arrangements of plasma charge. In particular, the analbuminemic rats balanced their reduced albumin charge with a reduced plasma strong ion difference (SID). This seemingly simple observation carries important implications. Perhaps most important is that the reduced SID represents a homeostatic adaptation to reduced plasma weak acid change (principally albumin), instead of a mixed acid-base disorder. Recognizing this adaptive mechanism allows the clinician to refrain from attempting to "repair" an unrecognized balanced acid-base state, reducing iatrogenically induced deranged physiology.

An important accompaniment to the reduced SID is an increase in unmeasured anions identified as the strong ion gap (SIG). While the origin of the unmeasured anions remains opaque, their presence is undeniable. An increased SIG correlates with early mortality after injury,[5] but its significance in the baseline steady-state of the analbuminemic rats is less morbid, and likely represents an appropriate baseline for reduced plasma weak acids in the absence of pathology. It is a straightforward extension to apply the Stewart approach to interrogate hypoalbuminemic patients in the ICU prior to therapeutic decision making with regard to acid-base balance, and a calculator is available on the Internet.[6] The authors are to be congratulated on further defining the mechanisms underpinning acid-base balance and guiding future clinical study. Accordingly, translating their data into clinical practice is straightforward with regard to understanding the components of normal and deranged pH. The extension to abandoning albumin supplementation to buttress buffer base is strongly supported by their data, but will likely require human data to convince current users prior to putting the final nail in the coffin.

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Maintaining Therapeutic Anticoagulation

The Importance of Keeping "Within Range"

Oral anticoagulation (OAC) is widely used in elderly patients for a variety of conditions, including atrial fibrillation (AF), valve replacement, and venous thromboembolism. In AF, OAC therapy has been proven to reduce the risk of all-cause mortality, stroke, and thromboembolic events.[1] However, the efficacy of OAC depends on maintenance of the international normalized ratio (INR) within the designated therapeutic range. Indeed, analysis of stroke or systemic embolism event rates in subjects allocated to the OAC arms in the initial primary prevention trials[2] found that these events occurred at subtherapeutic INRs, leading to the suggestion that "truly" therapeutic OAC (100% within target INR range) could reduce strokes by $\geq$ 85% in AF.

However, control of INR is beset by a large number of problems inherent to vitamin K antagonists that are heavily influenced by drug-drug and food-drug interactions, alcohol consumption, hepatic dysfunction, genetic variation in enzyme activity, and dietary intake of vitamin K.[3] Further, vitamin K antagonists have an intricate pharmacokinetic profile, with a slow onset/offset of action, which varies considerably within and between patients, requiring regular venepuncture to ensure that a therapeutic INR is maintained, with dose adjustment where appropriate.[4] Maintenance of this narrow therapeutic INR range is important because there is an increased risk of hemorrhagic stroke with INR $>$ 3.0 and thromboembolic complications at INRs $<$ 2.0.[5,6]

Thus, maintenance of INR within the therapeutic range is difficult. Even enthusiastic patients (and study doctors/nurses) within a clinical trial setting resulted in therapeutic INRs in approximately 60%.[7] A recent systematic review[8] also revealed that patients who receive long-term OAC achieve a therapeutic INR only 55% of the time. This is an alarming figure given that even a 10% time out of the therapeutic range has been associated with an increased risk of mortality (odds ratio, 1.29; $p < 0.001$), ischemic stroke (odds ratio, 1.10; $p = 0.006$), and other thromboembolic events (odds ratio, 1.12; $p < 0.001$) among patients receiving long-termc OAC for nonvalvular AF.[9]

In the current issue of *CHEST* (see page 1508), van Walraven and colleagues[10] determine the number of hemorrhagic and thromboembolic complications that could be avoided in elderly people ($>$ 65 years old) by maintaining a therapeutic INR. They show that hemorrhagic and thromboembolic risk increased significantly when INRs were $>$ 3.0 or were $<$ 2.0, respectively, and by maintaining the INR within the range of 2.0 to 3.0, 25.6% and 11.1% of anticoagulated-related hemorrhagic and thromboembolic events, respectively, could be prevented. Thus, if INRs could be maintained in the therapeutic range of 2.0 to 3.0, 1 in every 4 hemorrhagic events, and 1 in every 10 thromboembolic events could be avoided.[10]

The present study[10] is the first true population-based study of OAC control that attempts to reduce patient selection bias, but as with all studies based on retrospective analyses using databases, some misclassification of events may have occurred as a result of miscoding, as indeed was the case with stroke. In addition, any fatal events occurring prior to hospitalization were not recorded or included. This may have resulted in an underestimation of the number of events. Again, OAC exposure was recorded from databases, and if people did not refill a prescription within 100 days they may have not been included in this analysis. In addition, this cohort did not include people who were self-monitoring, had no INR monitoring or had their INR done at a laboratory outside of the study area, or those with INRs which were persistently $<$ 1.5, resulting in an possible underestimation of the true event rate.

The most recent guidelines of the American College of Chest Physicians[11] recommend different target INR ranges for patients prescribed OAC depending on the indication for which it is prescribed, although for the majority of indications the therapeutic INR range is 2.0 to 3.0, with slightly higher INRs for patients with mechanical prosthetic and bioprosthetic heart valves. While the current analysis by van Walraven and colleagues[10] did consider only hemorrhagic events occurring with INR $>$ 3.5 for people with previous valvular repair, they did not adjust for the indication for which OAC therapy was prescribed and therefore the corresponding INR target range. Consequently, not all the patients receiving a prescription for OAC included in the analysis by van Walraven et al[10] will have needed

to maintain their INR between 2.0 and 3.0; as such, some hemorrhagic events occurring with INR > 3.0 may not have been as a result of extreme anticoagulation and may have lead to an overestimation of the hemorrhagic event rate.

The current article also does not examine or adjust for concomitant medication, particularly with antiplatelet therapy and nonsteroidal antiinflammatory drugs, which have been shown to place patients at increased risk of bleeding. A retrospective analysis[12] in the United States of patients prescribed warfarin revealed that concurrent antiplatelet therapy was associated with a 53% increased of bleeding events. Recent practice guidelines[13,14] encourage the use of warfarin for patients at moderate-to-high risk for stroke, but the need for concomitant antiplatelet therapy, particularly for patients with coronary heart disease (CHD) and after percutaneous coronary intervention (PCI), increases the risk of bleeding and complicates decisions about treatment. In the recent UK evidence-based guidelines[14] for AF management issued by the National Institute for Health and Clinical Excellence, the assessment of bleeding risk was emphasized as part of the clinical assessment for thromboprophylaxis, with particular attention paid to the following patients: age > 75 years; those receiving antiplatelet drugs (*eg*, aspirin, clopidogrel), nonsteroidal antiinflammatory drugs; those receiving multiple drug treatments (polypharmacy); those with uncontrolled hypertension; those with a history of bleeding (*eg*, peptic ulcer or cerebral hemorrhage); and those with a history of poorly controlled anticoagulation therapy.

There is a paucity of data, however, pertaining to the optimal treatment of patients requiring OAC for non-valvular atrial fibrillation, or valvular repair, but who also have CHD or have undergone PCI. Aspirin and/or clopidogrel are now recommended for secondary prevention following acute coronary syndromes or insertion of a coronary stent, with the duration of therapy dependent of the type of stent deployed.[15] Aspirin plus warfarin therapy and "triple therapy" with aspirin, clopidogrel, and warfarin are associated with more bleeding complications,[15] with little impact seen on stroke and vascular events by the addition of aspirin to OAC in AF patients.[16]

Despite the wealth of scientific evidence advocating the use of OAC to reduce the risk of thromboembolic complications, such therapy is often underutilized because of the perceived increased risk of bleeding associated with OAC, particularly among elderly patients. Just as we stratify patients to receive OAC or not based on stroke risk, we should also determine our treatment strategy based on their risk of significant bleeding. Various factors have been identified as placing patients on OAC at greater risk of bleeding, including increasing age, female gender, high BP, anemia, previous myocardial infarction, cerebrovascular disease, concomitant medication use, particularly antiplatelet therapy, and history of previous bleeding.[17–19] The most recent bleeding risk stratification scheme[19] proposes bleeding risk stratifying for elderly patients (> 65 years old) receiving warfarin and includes eight variables to ascertain a patient's bleeding risk, demonstrating bleeding rates of 0.9%, 2.0%, and 5.4% for the low-risk, moderate-risk, and high-risk patients, respectively.[19] The ability to estimate bleeding risk among the elderly, who are often denied OAC but who stand to benefit more given their increased risk of stroke and mortality associated with advancing age, could help to improve the number of people offered OAC by calculating the benefit offered by OAC against the risk of significant bleeding.

Nonetheless, the success or failure of OAC therapy is to some extent dependent on the patients' understanding of the need for OAC, and the importance of maintaining the INR within the therapeutic range. Research[20] has demonstrated that many patients receiving OAC are not even aware of the risks associated with such therapy. Education[21] and self-monitoring of the INR with dose adjustment[8,22,23] have been shown to improve the percentage of time spent in the therapeutic INR range and to reduce the frequency of major bleeding in older patients commencing long-term OAC therapy.[22] However, while some patients are able to self-monitor and self-adjust their OAC therapy, many others are not.

Indeed, a recent systematic review and metaanalysis[23] of 14 randomized trials of self-monitoring of oral anticoagulation revealed that self-monitoring alone was associated with significant reductions in major hemorrhage (odds ratio, 0.65; 95% confidence interval, 0.42 to 0.99), thromboembolic events (odds ratio, 0.45; 95% confidence interval, 0.30 to 0.68), and all-cause mortality (odds ratio, 0.61; 95% confidence interval, 0.38 to 0.98). Randomized trials[23] that combined self-monitoring with self-adjusted OAC therapy also demonstrated a significant decrease in death and thromboembolic events, but not major hemorrhage. Further, a centralized telephone service run by a pharmacist, providing dose adjustment, improved INR control and reduced the risk of OAC-related complications compared to usual care offered by the primary care physician.[24] These are treatment options that should be considered and offered to appropriate patients given the significant improvements in INR control and decreases in adverse hemorrhagic, thromboembolic, and fatal events.

In conclusion, we must offer OAC therapy on the basis of a comprehensive assessment of stroke and bleeding risk. However, maintaining the INR in the therapeutic range 100% of the time will be virtually impossible, but we should optimize the conditions

that have demonstrated tighter INR control and offer tailored OAC therapy.

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Is Brachial Artery Peak Velocity Variation Ready for Prime Time?

The assessment of intravascular volume status is important in the ICU, since adequate resuscitation is critical for optimizing tissue energy supply, whereas excessive fluid may worsen outcome.[1,2] Rather than a single variable, detailed knowledge of a patient's underlying physiology and careful consideration of concomitant organ function must be put together into the whole clinical picture to determine if a patient needs fluid.

One variable that is crucial for determining who needs fluid is whether or not the patient can respond with an increased cardiac output to fluid infusion. While traditionally central venous pressure (CVP) and pulmonary artery occlusion pressure (wedge) have been used by clinicians to determine whether or not to administer fluid, numerous studies[3,4] have shown that cardiac filling pressures in isolation are often misleading when used to predict the effects of volume expansion on cardiac output.

There is increasing interest in the use of respiratory variations in vascular pressures (CVP, arterial and wedge pressure) to predict the cardiac output response to a fluid challenge. In patients receiving mechanical ventilation with *no* spontaneous efforts, continuous monitoring consistently demonstrates an early inspiratory rise in arterial pressure[5] ("reversed pulsus paradoxus"[6]), which is followed during late inspiration and expiration by a decrease in systolic pressure. Perel and Segal[5] defined the difference between maximum and minimum arterial systolic pressure during a respiratory cycle as *systolic pressure variation*. The inspiratory increase in pressure relative to the value at end-expiration was called *dUp*, and the fall in pressure relative to the end-expiratory value was called *dDown*. While dUp reflects a direct mechanical effect of positive pressure on the ventricle, dDown is an index of preload reserve. The larger the dDown and pressure variation, the greater the predicted increase in cardiac output with volume loading. Based on similar considerations on the interplay between respiration and stroke volume, other variables such as stroke volume variation (SVV),[4] which can be measured by the commercially available PiCCO system (PiCCO *plus*; Pulsion Medical Systems; Munich, Germany), or aortic blood velocity variation (ABVV)[3] have been shown to predict the hemodynamic effects of volume expansion on cardiac output as well. Basically, all of these new techniques (pulse pressure variation [PPV], SVV, ABVV) are predicated on the observation that the magnitude of the cyclic variation in stroke volume depends on whether the patient is operating on the steep or the flat portion of the Frank-Starling curve; that is, whether the heart is preload responsive or not.

While the superiority of respiratory variations of dynamic hemodynamic variables over static indicators in predicting fluid responsiveness has been demonstrated, several physiologic aspects must be considered to avoid misinterpretations. Breathing affects left ventricular (LV) stroke volume by changing independently LV filling and emptying.[7–9] Positive pressure in the thorax decreases preload and increases afterload on the right ventricle (RV).[10] The accompanied inspiratory decrease in RV stroke volume during positive pressure ventilation decreases subsequent LV preload and stroke volume, usually reaching its nadir during expiration. Conversely, during rapid intrathoracic pressure changes, LV stroke volume usually increases with pleural pressure.[9] The early inspiratory increase in LV stroke volume observed during PPV may be the consequence of enhanced pulmonary venous return, increased LV compliance because of decreased RV dimensions, decreased LV afterload, and/or external pressure on the LV.

Aortic elastance is an important variable that directly determines aortic pressure and flow. Elastance of the aorta is curvilinear, so that change in pressure for a change in volume positively correlates with initial aortic volume. Thus, blood that enters at a high initial aortic volume will produce a larger pulse pressure than if it enters at a lower initial volume. Aortic elastance varies with age and disease as does the relationship of stroke volume to pulse pressure.[11] For a given cardiac output, stroke volume also varies with heart rate and therefore so will pulse pressure.[12]

Thus, the relationship of stroke volume to pulse pressure differs widely between and within patients, and this greatly limits quantitative predictions. The variability of pulse pressure responses to a given stimulus should be particularly high in the population of critically ill patients, since several variables that affect stroke volume and aortic elastance (heart rate, chest wall compliance, or treatment with vasoactive drugs) vary considerably between critically ill patients. Notably, the predictive value of variables derived from stroke volume on volume responsiveness is valid only when patients have regular rhythm, do not have any spontaneous inspiratory or expiratory efforts,[13–15] and are receiving ventilation with same parameters as used in original studies. Deep sedation and/or neuromuscular blockade are therefore required to avoid spontaneous ventilation-related artifacts.

Nevertheless, data indicate that PPV and aortic blood flow variation are sensitive parameters for qualitative prediction of the response to volume infusion in patients receiving mechanical ventilation.[11] In this issue of *CHEST* (see page 1301), Brennan and coworkers[16] compared the correlation between brachial artery velocity variation (BAVV) and radial artery PPV and found that these variables correlate quite well. This observation is of interest because assessment of BAVV is a noninvasive approach, and the authors report that minimal training is required to accomplish reliable BAVV measurements. If it would be possible to develop a device that allows continuous measurement of respiratory

changes in brachial artery blood flow, resuscitation with fluid infusions could potentially be guided by using noninvasive techniques.

However, the study of Brennan et al[16] has some limitations. Firstly, the authors did not compare BAVV, their proposed measure of volume responsiveness, to a clinically relevant end point such as cardiac output or end-organ perfusion, and did not assess actual response of BAVV to volume challenge. Thus, although the correlation between brachial artery peak velocity variation and PPV is interesting, one could argue that the authors are assessing one surrogate marker for another surrogate. Secondly, the authors took their cutoff point used for comparison (PPV of 13%) from a study of patients with sepsis. However, because pulmonary and vascular compliance affect PPV, the 13% cutoff may not be widely generalizable. Thirdly, Bland-Altman analysis revealed that clinically meaningful variation does exist between BAVV and PPV for individual patients. Thus, whether specific patients would be mismanaged based on BAVV is unclear. Finally, the premise that noninvasive measures are preferable to invasive ones is certainly true; however, patients who require heavy sedation and/or paralysis should probably receive an arterial line. Therefore, the applicability of this noninvasive technique could be questioned.

We should use lessons from the past and not waste the clinical value of "new" parameters by improper use. The pulmonary artery catheter has been used for cardiac output measurement for > 30 years, and a study[17] suggests that physicians' knowledge in this area is still inadequate. In addition, the end point volume responsiveness *per se* is problematic, since such studies fail to identify patients who need fluid as opposed to those who may respond to fluid.

To evaluate if BAVV as a viable method for managing ICU patients, effects of BAVV-guided volume challenges on clinical outcome must be rigorously studied. Brennan et al[16] are commended on taking the first step.

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