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Weakness acquired in the cardiac intensive care unit: still the elephant in the room?

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Over the past two decades, the cardiac critical care population has shifted to increasingly comorbid and elderly patients often presenting with non-primary cardiac conditions that exacerbate underlying advanced cardiac disease. Consequently, the modern cardiac intensive care unit (CICU) patient has poor outcome regardless of left ventricular ejection fraction. Importantly, delayed liberation from organ support, independent from premorbid health status and admission severity of illness, has been associated with increased morbidity and mortality up to years post-general critical care. Although a constellation of several acquired morbidities is at play, the most prominent enactor of poor long-term outcome in this population appears to be intensive care unit acquired weakness. Although the specific burden of ICU-acquired morbidities in CICU patients is yet to be clearly defined, it seems unfathomable that patients will not accrue some sort of ICU-related morbidity. There is hence an urgent need to better establish the exact benefit and cost of resource-intensive strategies in both short- and long-term survival of the CICU patient. Consequent and standardized documentation of admission comorbidities, severity of illness indicators, relevant ICU-related complications including weakness, and long-term post-ICU morbidity outcomes can help our understanding of the disease continuum and how to better care for the CICU survivor and their families and caregivers. Given increasing budgetary pressure on healthcare systems worldwide, interventions targeting CICU patients should focus on improving patient-centred long-term outcomes in a cost-effective manner. It will require a holistic and transmural continuity of care model to meet the challenges associated with treating critically ill cardiac patients in the future.

Keywords ICUAW • Long-term legacy of critical illness • Acquired frailty • Patient-centred long-term outcomes • Diaphragm dysfunction • ECLS outcomes • Cost-effectiveness of cardiac critical care

Introduction

The core business of critical care cardiologists has changed considerably since the inception of the coronary care unit for management of arrhythmias and shock complicating acute myocardial infarction (AMI). Prioritized revascularization in acute coronary syndromes and multidisciplinary transmural heart failure management have transformed the epidemiology of acute cardiac disease and its care. Over the past two decades, the cardiac critical care population has shifted to increasingly comorbid and elderly patients often presenting with nonprimary cardiac conditions that exacerbate underlying advanced cardiac disease, notably heart failure and valvular disease.[1,2] Consequently, the modern cardiac intensive care unit (CICU) patient appears to have poor outcome regardless of left ventricular ejection fraction.[3] It is well understood that comorbidity impairs long-term outcome and, in the face of acute severe illness, predisposes to perpetuating multi-organ failure.[4,5] What has received comparably little attention in cardiac critical care literature is the finding in medical and surgical ICU populations that delayed liberation from organ support, independent from premorbid health status and admission severity of illness, associates with increased morbidity and mortality up to years post-critical care.[6,7] Although a constellation of several acquired morbidities is at play, the most prominent enactor of poor long-term outcome appears to be intensive care unit acquired weakness (ICUAW). While general critical care societies have termed critical care survivorship as their professions' defining challenge for the 21st century,[8] long-term post-CICU morbidity and mortality outcomes still need to be charted. This editorial discusses the mortgaging

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impact of prolonged critical illness on long-term post-ICU outcome, the critical role of ICUAW, and how this increasingly prevalent acquired frailty syndrome will challenge cardiac critical care practice logistically, ethically, and financially.

Intensive care unit acquired weakness and the legacy of prolonged critical illness

Intensive care unit acquired weakness: what's in a name?

Intensive care unit acquired weakness is a clinical syndrome reflecting dysfunction of the peripheral motor unit. It has been formally defined as the rapid loss of muscle mass and contractile force of skeletal muscle that has no cause other than critical illness.[9,10] Although described as early as 1892, the pathophysiology of ICUAW remains elusive. Animal models, post-mortem studies on diaphragm and peripheral nerve biopsies, and in-ICU collected samples of skeletal muscle have illustrated two patterns: myopathic (critical illness myopathy) and neuropathic (critical illness neuropathy). Myopathic changes structurally comprise preferential myosin loss, which is clearly distinctive from pure disuse atrophy affecting actin and myosin equally.[11–15] These changes have been attributed to induced atrogenes and an imbalance between anabolism and catabolism. Neuropathy involves axonopathy with endoneurial inflammation,[16,17] which in muscle biopsies translates into small muscle fibres, fibre-type grouping, and fibre group atrophy.[18] In addition to muscle atrophy, possible causes of neuromyopathy affecting the critically ill include direct toxicity of cytokines and endotoxins, disrupted microcirculation, altered neuronal and sarcolemma excitability, mechanical silencing, increased production of reactive oxygen species and energy stress,[19,20] and deficient autophagy.[19,20] *Figure 1* summarizes a pathophysiological construct for ICUAW, with indication of which factors might be more relevant to the CICU population.

Who is at risk

The incidence of weakness increases with increasing age, severity of illness, longer duration of mechanical ventilation and associated immobilization, and use of neuromuscular blockers and corticosteroids.[21–26] Sepsis, shock, and/or use of vasopressors are additional important predictors for ICUAW.[21–23,25] Glycaemic control and nutritional strategy are ICU-related factors that can be readily modified, and it has been shown that avoiding hyperglycaemia and avoiding parenteral nutrition while allowing a macronutrient deficit up to 1 week of critical illness are associated with less weakness.[21,25,27] Respiratory muscle weakness often co-exists with peripheral weakness, although overlap is not complete and respiratory weakness may even be more common.[28,29] Major risks factors for respiratory muscle weakness include sepsis and immobilization of the diaphragm during controlled mechanical ventilation. Overassistance, underassistance, and excentric loads due to patient-ventilator dyssynchrony may all induce diaphragm atrophy and weakness.[29]

Diagnosing intensive care unit acquired weakness

Establishing the presence of muscle weakness in a critically ill patient starts with an assessment of the Medical Research Council (MRC) sum score, quantifying isometric muscle strength in six muscle groups of upper and lower limb bilaterally, with a maximal total of 60. Critically ill weak patients classically demonstrate symmetric flaccid paresis of arms and legs, which may be so severe that they cannot overcome gravity (2/5) or make any visible nor palpable contraction at all (0/5). The MRC sum score has shown consistent interrater reliability and association with both short and long-term adverse outcome in ICU populations.[9,25,30,31] A score of 48 or less in the ICU indicates prognostically relevant weakness in the short-term, as this threshold stratifies risk for prolonged ICU and hospital stay, as well as delayed liberation from mechanical ventilation.[31] Furthermore, even a small reduction in the MRC at ICU discharge independently associates with increased mortality and reduced muscle strength, physical function and quality of life up to 5 years post-ICU discharge.[32,33] Its reliability, feasibility and prognostic relevance have made the MRC sum score the gold standard for diagnosing weakness in the ICU over other functional assessments such as hand grip strength dynamometry, which does not reflect global muscle function and is prognostically related mostly to short-term outcome.[20,34]

Nerve conduction studies and electromyography do not require cooperation and are valuable investigations that, in addition to neuraxial imaging and/or sampling, muscle biopsy, and serology, are used in a more targeted fashion to exclude alternative causes of muscle weakness that might warrant specific treatment (e.g. Guillain–Barre syndrome).[10] Classic nerve conduction studies in ICUAW demonstrate loss of compound muscle action potential (CMAP) amplitude without significant changes in conduction velocity, although increased CMAP duration has been reported and complete loss of muscle signal can result in conduction block.[35] Electromyography can reveal spontaneous electrical activity indicating active denervation, and if patients are awake and cooperative, recruitment patterns can help point towards neuropathy or myopathy underlying weakness.[35–37] Abnormal electrophysiological findings in the ICU have consistently been associated with short-term morbidities including prolonged duration of mechanical ventilation, ICU and hospital stay and physical impairments prior to hospital discharge, as well as with poor long-term survival.[33,38,39] The few electrophysiological follow-up studies available suggest that myopathic patterns are most commonly observed and tend to resolve faster and more completely as compared to neuropathy.[40–43] Simplified protocols assessing single nerve conduction can help support a clinical suspicion of critical illness neuromyopathy.[38,44,45] Direct muscle stimulation, an integrated interrogation of the peripheral motor unit, has shown potential to increase discriminative power of electrodiagnostic studies for critical illness neuropathy vs. myopathy.[46–48] This time-consuming investigating is currently only used in research and unlikely to enter daily practice soon as the distinction between neuro- and myopathy currently has no implications for patient management.

Temporal assessment of quadriceps thickness, by ultrasound, CT, or MRI, has been suggested as a non-invasive measure of quantifying muscle wasting and as a surrogate for weakness in unconscious patients. However, interpretation of findings should be done with caution as muscle strength cannot be simply deduced from muscle mass and, especially for quadriceps ultrasound, there is a lack of standardized protocols with consequently inconsistent findings on reliability. Furthermore, there is no clear association with long-term outcomes.[49–52] As such, these assessments are mostly limited to a research context or used to rule out other diagnoses (e.g. MRI for myositis), as they do not steer medical management otherwise.

Failure to liberate a patient from mechanical ventilation may be the first manifestation of ICU-acquired diaphragm dysfunction, and mechanical ventilation itself can facilitate diaphragm injury in case of an unfavourable balance between respiratory load and muscle capacity.[53–55] Structural and functional alterations of the diaphragm are associated with poor clinical outcomes even when corrected for peripheral muscle weakness.[28,29,54,56,57] Consequently, dedicated assessment of diaphragm function, alongside respiratory drive and global respiratory effort, is valuable in the diagnostic and prognostic work-up of patients who are difficult to wean from mechanical ventilation and key to the emerging concept of diaphragm protective ventilation.

Spontaneous breathing depends on respiratory drive, which can be assessed during the first 100 ms of inspiration by measuring the airway

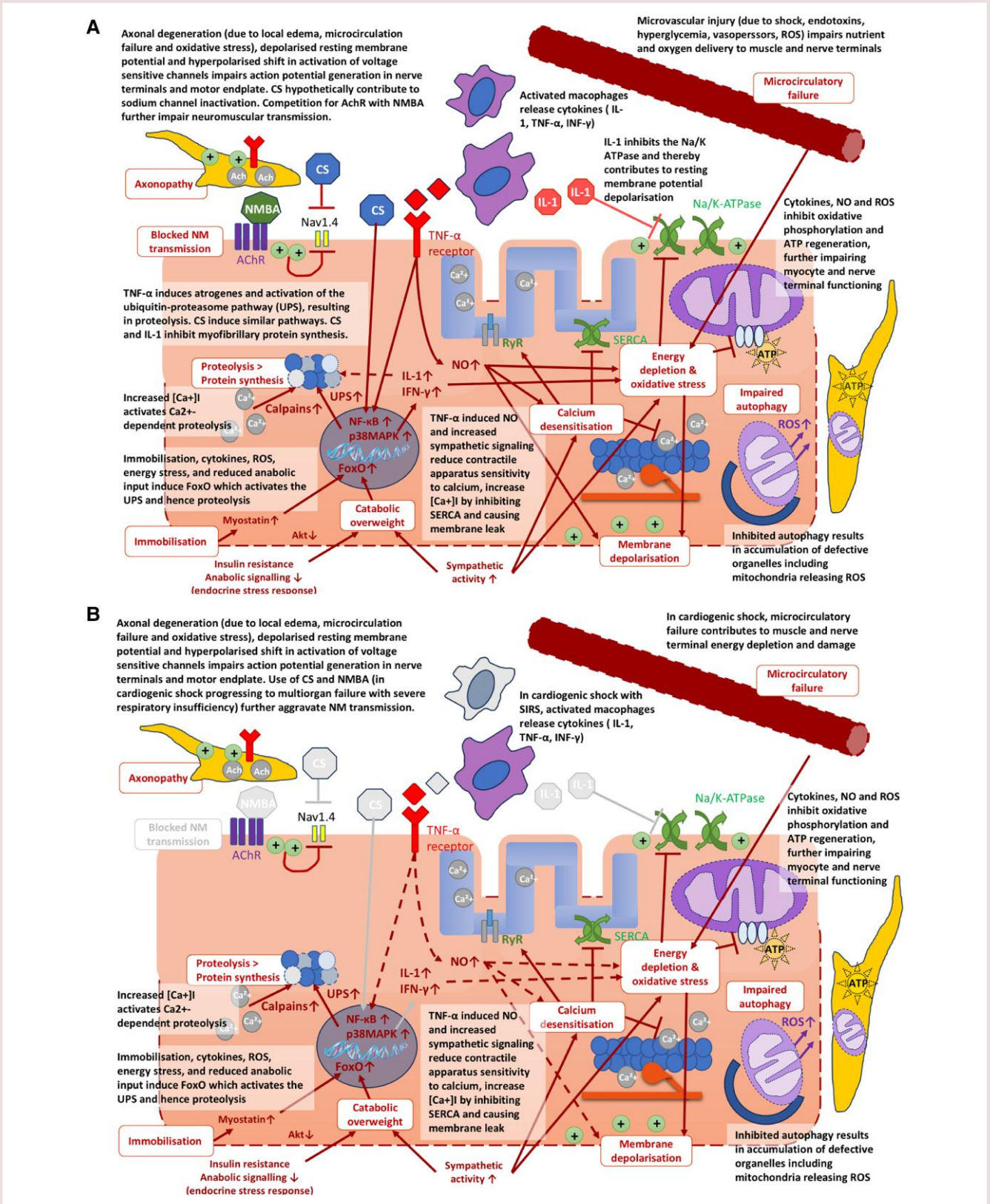

Figure 1 Pathophysiology of ICUAW and aspects of relevance for the CICU population.

pressure change starting from an end-expiratory occlusion (P0.1), as this initial inspiration phase is independent of pulmonary mechanics or diaphragm function.[55] Airflow generation depends on the diaphragm's ability to contract and generate negative intrathoracic pressures.[58] The reference technique assessing diaphragm function is measurement of the transdiaphragmatic pressure derived from oesophageal and gastric manometry using a dual balloon catheter, either during a volitional maximal inspiratory manoeuvre,[59] using a unidirectional valve in patients unable to co-ordinate their inspiratory effort,[60] or by bilateral anterolateral magnetic stimulation of the phrenic nerves (BAMPS).[61] These techniques are invasive, require skill and may be expensive (BAMPS), hence alternatives have been explored. In conscious patients on mechanical ventilation, the airway pressure measured at the mouth during a maximal volitional inspiratory effort starting from end expiration is an easy, non-invasive, and prognostically relevant estimate of global inspiratory muscle function.[57,59,62] Diaphragm ultrasound is non-invasive bedside tool to specifically assess diaphragm function.[58,62,63] Patients with sufficient respiratory drive without ventilator support (either during a spontaneous breathing trial or during short disconnection from the ventilator) who demonstrate diaphragm excursion < 10–15 mm during tidal breathing have diaphragm weakness sufficient to explain weaning failure.[58,64,65] Diaphragm paralysis presents as paradoxical upper diaphragmatic excursion upon inspiration.[58] Variation in diaphragm thickness during the respiratory cycle (thickening fraction) also associates with weaning failure but clinical application hereof needs further validation.[29,63] Global inspiratory effort, or work of breathing, can be assessed by measuring the airway pressure swing during an end-expiratory occlusion manoeuvre lasting one respiratory cycle (Pocc).[53,55,66] Alternatively, using a dual purpose nasogastric tube equipped with electrodes (NAVA©), the electrical activity of the diaphragm (EAdi) can be continuously monitored, which allows assessment of innervation and neural drive, as well as diaphragm effort when combined with pressure estimates during end-expiratory occlusion manoeuvres.[54,55,66] An additional advantage of measuring EAdi continuously is that the signal can be used to trigger the ventilator, promoting patient-ventilator synchrony in supported ventilation modes, which may facilitate weaning.[66–68] Limitations include lack of reference values, and costs of the dedicated probes.

While data from physiological and observational studies support the concept of diaphragm protective ventilation, this framework needs to be validated in prospective studies. *Tables 1* and *2* summarise available validated tools and techniques to assess peripheral and respiratory muscle strength, and diagnose ICUAW.

Management of weakness

To date, there are no effective pharmacological interventions to treat ICUAW.[69] As the development of weakness is entangled in a complicated ICU trajectory, prevention of ICUAW depends on holistic critical care practice, including early goal-directed therapy for sepsis, infection prevention, and sedation stewardship.[70–72] In terms of nutrition, a 'less-is-more' approach seems most effective. Avoiding hyperglycaemia protects against the development of ICUAW but tight glycaemic control may have no added benefit in the absence of early parenteral nutrition.[21,27] Withholding parenteral nutrition during the first week of critical illness—thereby allowing a macronutrient deficit—results in less weakness than in an early PN strategy, and specific delivery of higher doses of protein does not improve strength and may even be harmful.[25,73–76] Early mobilization of critically ill patients was previously shown to improve functional recovery[77] as well as reduce the risk of weakness and cognitive disability at 1 year post-ICU.[78] These benefits could not be corroborated in further multicentre trials,[79,80] which sparked a recent scrutiny of available evidence. Meta-analyses suggest that early active mobilization in ICU likely reduces ICU and hospital length of stay, and improves patient reported physical function at 6 months post-discharge. Findings relating the impact on objective measures of strength and physical function measures were inconsistent. No substantial risk of in ICU adverse events was reported, although one randomized controlled trial (RCT) highlighted potential risks associated with overly aggressive protocols.[81–88] The high standards of physiotherapy as part of standard care in study protocols potentially limit the discovery of a statistically significant physical function increment in a population.[89] In ICU, physiotherapy success is possibly further affected by treatment modality (device use, timing, frequency, duration), prioritization and staff experience, and patient profile. It has been suggested that combining early mobilization with inspiratory muscle training might facilitate functional recovery and liberation from mechanical ventilation: the best modality remains to be identified but inspiratory muscle training of any sort seems superior to none.[90,91] The use of proportional assist modes for spontaneously breathing patients being liberated from mechanical ventilation while monitoring respiratory drive and effort holds promise to prevent diaphragm injury but further evidence is needed.[54,92] Attempts to remediate the effects of ICUAW post-ICU discharge have been mainly in the field of rehabilitation, showing no clear benefit, but available evidence suffers from heterogeneity, small sample size, and nonadherence in the long-term.[93,94] Further research on rehabilitation during and post-ICU, and treatment options for ICUAW in general, is warranted.

Post-intensive care syndrome: the cost of survivorship

Intensive care unit acquired weakness was shown to be a major driver of adverse post-ICU outcome, as it independently associates with prolonged ICU stay, prolonged duration of mechanical ventilation, and increased risk of ICU readmission.[31] Intensive care unit acquired weakness can have both resolving and worsening trajectories in the first year after hospital discharge, and while persisting weakness heralds even worse outcome, reduced muscle strength at the time of ICU discharge independently associates with increased mortality, worse physical function, and lower quality of life up to 5 years post-ICU discharge.[32,33]

Importantly, ICUAW is not an isolated feature in the prolonged critically ill. It usually presents alongside a myriad of acquired morbidities, including cognitive and mood disorders, physical and psychological trauma (scars, urinary incontinence, vocal cord dysfunction, post-traumatic stress disorder), and renal function impairment.[95] This accrued frailty is referred to as the post-intensive care syndrome (PICS) and mortgages a patient's outcome in the short- and long-terms. It is particularly frequent in those with a complicated ICU stay. In fact, one week of ICU is a critical threshold after which a patients' outcome disconnects from their admission diagnosis, and the accrued morbidity of the ICU stay becomes predictive of long-term outcome, further modulated by age and prior comorbidity.[6,7] In older (45–66 years) hospital survivors of prolonged mechanical ventilation, 75% of all days alive were spent in health care facilities or receiving home care, and at 1 year only 6% had returned to work and 27% experienced good quality of life.[4,6]

Critical care currently utilizes up to 1% of the gross domestic product of the USA, and this does not include the sustained inflated health care utilization of its survivors. Readmission rates of critical care survivors are high, in particular for those surviving prolonged mechanical ventilation and sepsis, who are often left weak (hospital readmission up to 50% and ICU readmission 20–30% within 1 year).[6] Post-discharge costs vary between 10 000 and 16 000 Canadian dollar (CAD) per patient per year depending on number of disabilities, with minimal decrease beyond the first year.[96–98] The cost per QALY for patients receiving mechanical ventilation for more than 1 week amounts to 85 000 CAD per patient, although the number varies considerably across patient profile (at 18 years of age, prolonged mechanical

Table 1 Available assessments of intensive care unit-acquired muscle weakness (peripheral) with normal values and critical thresholds when available as per key references in literature

Assessment domain		Method	Normal values Threshold for ICUAW or abnormal neuromuscular electrophysiology	Reference
Muscle strength	MRC sum score	Bedside semiquantitative (manual) assessment of isometric strength in six muscle groups of upper and lower limb bilaterally (arm abduction, forearm flexion, wrist extension, hip flexion, knee extension, foot dorsal flexion) in a cooperative patient	MRC sum score < 48/60. ie the sum of isometric strength subscores on the medical research council scale in six muscle groups of upper and lower limb bilaterally of 48 or below indicates significant muscle weakness MRC subscores: 0 = no visible/palpable contraction; 1 = visible/palpable contraction without movement of the limb; 2 = movement of the limb but not against gravity; 3 = movement against gravity but not against resistance; 4 = movement against gravity and resistance; 5 = normal	9,10
	Hand grip strength	Bedside quantitative assessment of isometric strength of the hand using dynamometry, in a cooperative patient with MRC subscore for both forearm flexion and wrist extension 3/5 bilaterally (measured in kg or Newton)	Normal values for hand grip strength have reference ranges for age, gender, and dexterity. In a population of middle-aged critically ill patients, accepted thresholds for significant weakness based on hand grip strength testing are: Males < 11 kg force Females < 7 kg force	30,34,162
Trophic state	Quadriceps ultrasound	(i) RF CSA, measured by planimetry, or (ii) RF MLT, measured on B-mode ultrasound image in a supine relaxed individual, perpendicular to the long axis of the thigh, halfway or 3/5 of the distance from the anterior superior iliac spine to the superior patellar border, minimizing soft tissue distortion	Normal values for quadriceps dimensions on ultrasound have reference ranges for age and gender. In cohorts of healthy middle-aged individuals (60 years, 45% male) normal ranges included the following RF CSA: 4.6 ± 1.4 cm^2 RF MLT: 2.4 ± 0.8 cm	163–167
Neurophysiology	NCS, single nerve	Measurement of the peroneal nerve (motor) CMAP	Abnormal nerve conduction response suggesting ICU acquired neuromyopathy can be identified if motor CMAP of the peroneal nerve < 0.65 mV (peroneal nerve)[a]	38,45,167
	NCS, integrated	(1) Assessment of neuromuscular junction block by repetitive stimulation of the median nerve (3 Hz) (2) Orthodromic conduction studies in motor nerves (ulnar and common peroneal nerves bilaterally) (3) Antidromic conduction studies in sensory nerves (ulnar and sural nerves bilaterally)	Abnormal nerve conduction response suggesting ICU acquired neuromyopathy can be identified by a combination of following findings, in the absence of decrement on repetitive nerve simulation (1) suggesting neuromyopathy: CMAP amplitudes < 80% of the lower limit of normal in two or more motor nerves without conduction block (>1 mV for peroneal nerve)[a] (2) suggesting neuropathy: SNAP amplitudes < 80% of the lower limit of normal in two or more sensory nerves (>10 μV for sural nerve)[a]	38,41,44
	Electromyography	(1) Screen for SEA, which can be done in uncooperative patients (2) Assess motor unit recruitment and interference patterns in patients able to perform volitional contractile efforts of a muscle group to distinguish neuropathy from	(1) SEA: sustained fibrillation potentials and/or positive sharp waves after initial insertional activity in at least two muscles of at least two limbs (active denervation) (2) Motor unit potentials with a low amplitude and	35–37

Continued

Table 1 *Continued*

Assessment domain	Method	Normal values Threshold for ICUAW or abnormal neuromuscular electrophysiology	Reference
	myopathy (performed unilaterally in one standard proximal and one distal muscle in both upper and lower limbs)	short duration and early rapid recruitment: myopathy	
Direct muscle stimulation	Using a combination of intramuscular and surface stimulation electrodes, the ratio of the motor CMAP evoked by nerve stimulation relative to the CMAP obtained via direct electrical stimulation of muscle is obtained	Abnormal direct muscle stimulation result suggesting either neuropathy or myopathy can consist of (1) ratio of motor CMAP evoked by nerve stimulation relative to that obtained via direct electrical stimulation of muscle neCMAP/dmCMAP < 0.5 is suggestive of neuropathy ratio of motor CMAP evoked by nerve stimulation relative to that obtained via direct electrical stimulation of muscle neCMAP/dmCMAP > 0.5 in combination with abnormal amplitude of motor CMAP by direct muscle stimulation is suggestive of myopathy	[46–48]

ICUAW, intensive care unit acquired weakness; MRC, Medical Research Council; RF CSA, rectus femoris cross-sectional area; RF MLT, rectus femoris muscle layer thickness; NCS, nerve conduction studies; CMAP, compound motor action potential; SNAP, sensory nerve action potential; SEA, spontaneous electrical activity; neCMAP, nerve evoked compound motor action potential; dmCMAP, direct muscle stimulated compound motor action potential.
[a]Thresholds for abnormal CMAP and SNAP may differ depending on local neurophysiology laboratory reference values, and may be confounded by local factors (tissue oedema, interference from electrical equipment).

ventilation implied 14 000 CAD per QALY, at 75 years > 127 000 CAD per QALY, and at 85 years > 206 000 CAD).[99]

As the recent COVID-19 pandemic has shown, sustainability concerns of the health care system cannot dictate individual patient level decisions but should be taken into consideration for general policy guidance on critical care delivery.[100] The mental, physical and financial aftermath of critical illness, at both the individual and societal level, is of principal concern. Experts in the field have argued that, until a pathway to mitigate poor post-ICU outcome is available, surgeons and critical care givers should proactively engage in goals of care discussions prior to major surgery and ICU admission with patients at highest risk of the post-intensive care syndrome.[95] These conversations can be updated as admission unfolds, to ensure ongoing care and its expected outcomes are in line with the patients' values.

Intensive care unit acquired weakness in the contemporary cardiac intensive care unit: current knowledge and its gaps

Groups at risk and implications

The incidence of ICUAW is rarely if ever reported in CICU registries or trials, even though its risk factors among CICU patients, including mechanical ventilation, shock, and multi-organ failure, are skyrocketing.[2,101] Hypothetically, the incidence of weakness could be extrapolated from the medical and surgical ICUs to the CICU as their population distributions increasingly overlap. This implies that at least one-third and up to 80% of patients in CICUs receiving mechanical ventilation, renal replacement therapy, and mechanical circulatory support may develop weakness and suffer from its lasting morbidity and mortality impact. As this subgroup of patients admitted to the CICU is rising, cardiac care specialists need to familiarize themselves with holistic critical care principles to maximally avoid any iatrogenesis.[102]

Some patient populations, specific to the CICU setting, could be more vulnerable to the development and negative impact of ICUAW.

Muscle weakness is a well-known comorbidity affecting chronic heart failure (HF) patients.[103–105] Inspiratory and peripheral muscle weakness due to myofibre atrophy with specific myosin loss, increased ratio of type I to type II muscle fibres, and mitochondrial impairment lead to muscle metabolic inefficiency and altered metaboreflex resulting in physical function impairment often disproportionate to the degree of HF.[106–108] Additionally, premorbid muscle reserve likely determines the risk of developing weakness. Although the mechanisms of both ICUAW and persistent weakness in ICU survivors remain to be elucidated, it seems prudent to suspect vulnerability of HF patients to the added burden of ICUAW.

Patients presenting in cardiogenic shock (CS) frequently develop multi-organ failure requiring organ support, which increases their risk for weakness.[101,109] In the cardiometabolic (former 'warm and wet') CS clinical phenotype, not only microcirculatory failure but also higher levels of inflammatory cytokines implicated in the pathophysiology of ICUAW, including IL1 and TNF-α, could be at play.[110–112] A subgroup of particular interest is those CS patients requiring both mechanical ventilatory and circulatory support (MCS).[113] In acute respiratory distress syndrome (ARDS) patients, some expert centres aim to have patients on venovenous extracorporeal membrane oxygenation (vvECMO) awake and breathe independently (i.e. without excessive respiratory drive and consequent risk of patient-inflicted lung injury) and even extubate such patients, facilitating active rehabilitation. Limited data available suggest that this strategy might be feasible in 20% of ARDS patients, however, there is no definitive data on the relative costs vs. benefits of weaning mechanical ventilation first, as apposed to

Table 2 Available assessments of intensive care unit-acquired muscle weakness (respiratory, on mechanical ventilation) with normal values and critical thresholds when available as per key references in literature

Assessment domain	Measurement	Method	Normal values Threshold for respiratory/diaphragm weakness	Reference
Respiratory drive	P0.1[a]	Airway occlusion pressure: negative pressure during the first 100 ms of an inspiratory effort starting at end expiration (FRC)	1.5–3.5 cm H_2O	53–55
Respiratory effort	Pocc[a]	Expiratory occlusion pressure: maximal negative pressure during tidal breathing during the whole inspiratory effort starting at end expiration (FRC)	Less negative than −15 cm H_2O More negative than −3 cm H_2O (to avoid over- or underassistance)	54,55
Respiratory muscle function	MIP[b]	Maximal inspiratory pressure: airway pressure measured at the mouth during a volitional maximal inspiratory effort starting at end expiration (FRC)	Normal values for maximal inspiratory pressures have age and gender specific ranges. In a population of middle aged, critically ill patients, accepted threshold values for maximal inspiratory pressures indicating significant respiratory muscle weakness are the following: <83 cm H_2O (male) <62 cm H_2O (female)	62,168
Diaphragm function	ΔPdi[c]	Inspiratory swing in transdiaphragmatic pressure (using oesophageal and gastric manometry) during (i) volitional maximal inspiratory manoeuvre, (ii) end-expiratory unidirectional valve closure, and (iii) supramaximal phrenic nerve stimulation with BAMPS in uncooperative patients (also referred to as twitch transdiaphragmatic pressure or Pdi,twitch)	• During assisted spontaneous breathing: swing in transdiaphragmatic pressure using oesophageal and gastric manometry should be <10–15 cm H_2O and >3–5 cm H_2O (to avoid over- or underassistance) • During phrenic nerve stimulation: swing in transdiaphragmatic pressure using oesophageal and gastric manometry, Pdi, twitch < 20 cm H_2O indicates significant diaphragm weakness	60–62,168
	Diaphragm ultrasound[d]	(1) Direction and amplitude of diaphragm excursion (2) Relative thickening of the diaphragm (thickening fraction) during unassisted inspiration, measured in M-mode	Reference values are gender specific and dependent on side of measurements (1) Inspiratory excursion < 10–15 mm (2) Inspiratory thickening fraction < 20% (<25–33% predicts weaning failure)	54,58,62,63,169
Diaphragm innervation	Phrenic NCS[e]	Stimulation of phrenic nerve using surface electrodes applied near the cervical head of the sternocleidomastoid muscle	Normal phrenic nerve action potential amplitude: 0.67–1.11 mV	170
	EAdi[c]	Diaphragm electrical activity, reflecting neural respiratory drive	Normal EAdi > 10 μV	54,171

P0.1, airway occlusion pressure; Pocc, expiratory occlusion pressure; MIP, maximal inspiratory pressure; ΔPdi, inspiratory swing in transdiaphragmatic pressure; BAMPS, bilateral anterolateral magnetic stimulation of phrenic nerves; EAdi, electrical activity of the diaphragm.
[a]P0.1 and Pocc can be measured on any ventilator during assisted spontaneous breathing through expiratory occlusion.
[b]MIP requires a manometer attached to the endotracheal tube, and depends on a patient's ability to consciously perform a maximal inspiratory effort.
[c]ΔPdi and EAdi require oesophageal placement of measuring equipment, i.e. either a dual balloon nasogastric catheter with manometers in the oesophagus and stomach, or a nasogastric tube equipped with electrodes. Measurements can be obtained without a patients' conscious contribution, although sophisticated material is required if maximal diaphragm function is to be determined in an uncooperative patient (i.e. BAMPS).
[d]Diaphragm ultrasound can be performed with any low frequency (2–5 MHz abdominal/cardiac transducer, for subcostal approach) or high frequency (7–12 MHz linear transducer, for intercostal approach) probe although some training is required to properly visualize and estimate excursion and thickening.
[e]Phrenic NCS require dedicated equipment and expertise, and hence availability may be highly centre dependent.

weaning vvECMO first.[114–116] Encouraging observational data in patients bridged to lung transplant showed that awake vvECMO had better transplant outcomes as compared to patients who remaining sedated and intubated.[117,118] Although causality of the awake strategy in improving post-transplant outcome is difficult to prove, this strategy might be worth exploring in CICU patients on mechanical circulatory support, especially when bridged to left ventricular assist device (LVAD) or heart transplant.

Post intensive care syndrome in cardiac intensive care unit survivors

Long-term CICU outcome data are relatively scarce, but available evidence suggests similarly bleak prospects as reported in other critically ill patient cohorts.

Need for recurrent hospitalization in HF irrespective of ejection fraction is a dreaded evolution, as long-term mortality rises almost exponentially in patients admitted for HF relative to patients managed in the community.[119] These high mortality rates might be explained by a chronic stressed output state predisposing patients to deconditioning and increased vulnerability to destabilizing effects of infections or illness, creating a revolving door effect. Mortality is highest in HF patients requiring CICU admission, with a median survival of under a year in a cohort recruited in community CICU's in the USA.[120] In this cohort, estimated 5-year survival in hospital survivors was 20%. Interestingly, LVEF was not predictive of mortality, a finding consistent across critically ill HF populations. As patients with HF admitted to an CICU have high rates of utilization of critical care therapies, often exceeding 50%,[2,3] it seems likely that multi-organ failure and its treatments modulate this adverse outcome. Durable left ventricular assist devices are the sole mechanical circulatory support devices that have shown improved survival and quality of life in HF progressing to intolerable rest symptoms or inotropic dependency, but outcome is poor for patients in CS. With early analyses estimating costs at $200 000 per QUALY, cost-effectiveness of LVAD has been questioned, although reassessment with the latest generation of devices that have better durability for less complications is pending.

In contemporary CICUs, 'only' 14% of ICU level of care is dedicated to the treatment of CS, but this syndrome carries an excessive mortality and financial burden.[2,109,121–124] Only 4–6% of AMI patients progress to CS,[125,126] but AMI remains the most prevalent cause of CS treated in the CICU. The prevalence of other aetiologies of CS, including ischaemic cardiomyopathy without acute coronary syndrome (18%), non-ischaemic cardiomyopathy (28%), and more rare causes (VT, valvular disease), is rising[109] and although these conditions are resource-intensive and patients have important comorbidities (more severe pre-existent HF, pulmonary hypertension, arrhythmias), in-hospital survival of non-AMI-CS is significantly better than in AMI-CS.[122,127] Based on European and North American registries, current in hospital mortality of AMI-CS is slightly <40%, which represents a significant decrease from 70–80% over the past two decades, mainly due to early culprit vessel revascularization.[109,123,126,128,129] Unfortunately, hospital survivors of AMI-CS still experience five-year mortality rates as high as 60%, without obvious plateau up to 10 years post-critical care.[101,130] This number far exceeds the 15% five-year all-cause mortality rates of AMI patients without CS, highlighting the morbidity of this syndrome. In a long-term follow-up cohort of over 9700 patients treated in Ontario for AMI-CS, predictors of worse 1-year survival included higher age, higher comorbidity on CICU admission, and more organ failure during CICU admission.[101] This illustrates the culmination of both preadmission frailty and critical care acquired morbidity in poor long-term outcome as seen in general critical care populations.[5] The association of MCS with worse outcome observed in this cohort may have been mediated by higher illness severity on admission or relative underutilization of the intravascular microaxial blood pump Impella© (2% of all MCS, majority being intra-aortic balloon pump) given lack of funding for this MCS modality in Canada, although a mediating or moderating effect of ICU-related morbidities cannot be excluded. Additionally, loss of independence post-CICU admission for AMI-CS is common. In the same cohort, 42% of AMI-CS hospital survivors required a higher level of care as compared with baseline, and 15% were discharged to a long-term care facility. This translated to a median 1-year health care cost of over 45 000 CAD per hospital survivor, ranging up to almost 80 000 CAD, with nearly a third of cost occurring after hospital discharge.[131] Furthermore, 48% of hospital survivors were readmitted to the hospital within 1 year,[101] inflating median 1-year health care cost per patient to 65 000 CAD and up to 100 000 CAD.[131] During the study time (2009–19), post-hospital mortality and home time of AMI-CS barely changed, reflecting failure of contemporary CICU management to improve long-term patient prospects notwithstanding an average individual inpatient care expenditure more than triple that observed for both AMI and HF hospitalizations in Canada.[131] The DanGer SHOCK trial is the first multicentre RCT to demonstrate benefit on intermediate term mortality (180 days) of AMI-CS using Impella© on top of standard care vs. standard care alone (46% vs. 59%, respectively) with a number needed to treat of 8.[132] The observed mortality benefit likely resulted from the management of carefully selected patients (only ST-segment elevation myocardial infarction (STEMI), <20% cardiac arrest, <15% SCAI-CWSG stage E) in experienced shock centres[132] as suggested by previous work focusing on the positive mortality impact of cardiogenic shock teams.[133] Although these findings are encouraging, absolute 6-month mortality remained high, and the 22% relative mortality risk reduction came at the cost of double the rate of renal replacement therapy utilization and triple the rate of sepsis, factors that have been associated with adverse long-term outcome in CICU cohorts.[134] One small study documenting one year outcome of Impella© noted increased one year health care costs per patient (88 000 CAD), mostly due to inpatient costs. Importantly, only 39% of hospital survivors were discharged home,[135] and 68% patients were transitioned to LVAD therapy, the cost of which was not included in the analysis. Before advocating liberal use of Impella© in the AMI-CS population, there is an urgent need to confirm meaningful improvement in long-term outcomes and prioritize the identification of predictors allowing for selection of patients that will benefit most.[109]

Survival after out of hospital cardiac arrest (OHCA) remains poor and is mostly determined by nature of the arrest and prehospital interventions, including bystander cardiopulmonary resuscitation, early response time by emergency medical services, and access to an automated external defibrillator.[136,137] In the context of STEMI, short-term survival and neurological outcome of OHCA improves when care is concentrated in cardiac critical care centres.[138] Nonetheless, most in hospital interventions have failed to improve outcome.[139] Despite equivocal evidence, several invasive treatments have permeated clinical practice, including targeted temperature management in the first 48–72 h post-arrest[140–143] and extracorporeal life support. A recent meta-analysis showed that 10-year survival of those admitted to the hospital or ICU remains unsatisfactory (28%) but improved to 68% in those surviving to hospital discharge or 30 days after OHCA.[144] Although neurological outcome (usually expressed as cerebral performance category) is a major endpoint in studies on OHCA, objective cognitive function, physical function, and quality of life beyond 1 year are rarely reported. Available evidence at one year post-arrest is survey based: responders had quality of life scores (SF-12, PCS-SF-12, and EQ-5D) comparable to the average general population, high return to work rates (70%) and were mostly independent for activities of daily living.[145–149] Although highly promising, selection bias and underestimation of disability burden cannot be excluded, and a trend for younger patients to score significantly below their age-adjusted predicted values is of concern.[145]

Managing weakness in a contemporary cardiac intensive care unit

Perspective on the way forward

In response to the dramatic change in CICU patient demographics and their care needs, cardiac critical care societies have advocated for transformative changes at the level of staffing, organization, and daily practice

of the cardiac intensive care.[2,102,150] Incentivized by their improvement of cost-effectiveness and care quality in general critical care populations, branches of the European Society of Cardiology and American Heart Association have supported the adoption of a high-intensity staffing model[151–154] and implementation of protocols for prevention of infections, venous thromboembolism and stress ulcers, and management of nutrition, sedation, and weaning from mechanical ventilation.[102,155,156] Dedicated development of specialized care guidelines and provider teams relevant to the CICU population has started to show even long-term survival improvement.[133,138] The importance of future research focusing further on long-term patient-centred outcomes including measures of physical function and quality of life has been stressed.[109] Understanding the incidence of ICUAW and PICS in this population might leverage pathways to improved long-term outcome. Indeed, because the acute mortality of cardiac critical illness has decreased, critical illness-related complications such as ICUAW will become an important dictator of long-term outcome. Like transmural care pathways installed for heart failure management, the diagnosis of ICUAW should ideally prompt activation of a continuum of care pathway that allows patients to access care bundles appropriate to their individual needs, hopefully mitigating the risk of ongoing health care usage and loss of QUALYs.

Daily cardiac intensive care unit practice

In present day CICU practice, weakness is not routinely assessed, but this could be a relatively natural extension of the patients' head-to-toe assessment. Indeed, screening for neuromuscular problems constitutes an important part of patient monitoring in the CICU, as some warrant urgent intervention, including stroke, seizures, compression neuropathy, limb ischaemia, or neuromyopathies associated with adverse drug reactions (statin induced myopathy) or cardiac disease (autoimmune and immune checkpoint inhibitor mediated myositis associated with myocarditis). As part of protocolized care, early mobilization should become standard practice as it was shown to be feasible and safe even in the sickest of CICU patients.[157–159] Facilitating early mobilization implies a care strategy aiming for patients to be awake, oriented, and cooperative, which is known to have pleiotropic beneficial effects on patient-centred post-ICU morbidity outcomes including physical function and cognition. More common implementation of diaphragm ultrasound and monitoring/exploiting of diaphragm electrical activity during mechanical ventilation will facilitate research to determine the most optimal way to deliver lung- and diaphragm protective ventilation.[54,66] Implementation of bed cycling and inspiratory muscle training as part of research protocols in CICU could facilitate research to establish the impact of in ICU rehabilitation on both short- and long-term morbidity outcomes. Definitive evidence will rely on dedicated assessment of effects of dose, intensity and modality of physiotherapy in patients with or at risk of ICUAW. As part of a transmural care initiative, cardiac rehabilitation comprising of a combination of aerobic, resistance and inspiratory muscle training, was shown to improve aerobic exercise capacity and survival in HF patients with muscle weakness.[160] As reduced oxidative capacity has been implicated in the pathophysiology of ICUAW, specific effort to recruit those CICU survivors with weakness could potentially ameliorate their long-term prospects.

Post-cardiac intensive care unit outcomes

Despite increasingly advanced pharmacological and mechanical interventions pushing boundaries for support of acute heart failure, shock, and OHCA, this has not resulted in better long-term survival rates. Several factors are likely at play depending on the CICU patient at hand. For example, failure of implementation of optimal HF guideline directed therapy at the individual patient level tends to be a surrogate marker of the physiological instability of that patient. Concerns of renal failure, hyperkalaemia, and fall risk will only increase keeping the demographic evolution of our population in mind. The possibility of exacerbated multiple organ failure and prolonged critical care dependence adding to that burden of frailty, and further hampering prospects, should not be overlooked. As such, there is an urgent need to better establish the exact benefit and cost of resource-intensive strategies such as MCS in both short- and long-term survival of the CICU patient. It seems prudent to concentrate intensive cardiac critical care delivery in centres experienced at providing organ support including MCS for established indications, embedded in a research incentive to push the field forward.[161] Consequent and standardized documentation of admission comorbidities, severity of illness indicators, relevant ICU-related complications including weakness, and long-term post-ICU morbidity outcomes can help our understanding of the disease continuum and how to better care for the CICU survivor and their families and caregivers. Cardiac critical care research efforts should additionally focus on maximally utilizing observational data to help identify subgroups most likely to benefit from a specific intervention and dedicate costly RCTs to that goal.

Giving meaning

Awaiting those changes, CICU caregivers must reflect on the importance of informed consent and goals of care discussions in their patients. Although the specific burden of ICU-acquired morbidities in CICU patients is yet to be clearly defined, it seems unfathomable that patients will not accrue some sort of ICU-related morbidity and leave the CICU more frail than upon admission. Exploring a patient's goals of care becomes more vital than ever, as patients might choose to refrain from the certainty of physical and psychological suffering for both themselves and their families if return of profit is negligible by their standards and wishes.

Conclusion

Overall medical complexity dictates outcome of patients in the modern CICU. Appropriate management of this evolving patient population requires expertise in both general and cardiac critical care medicine. Strategies ensuring holistic approach in the care for and research of critically ill cardiac patients remain to penetrate the care landscape. Outcome studies and registries should aim to record and report both predictors and manifestations of short- and long-term morbidities including ICUAW. Given increasing budgetary pressure on healthcare systems worldwide, interventions targeting CICU patients should focus on improving patient-centred long-term outcomes in a cost-effective manner. It will require a holistic and transmural continuity of care model to meet the challenges associated with treating critically ill cardiac patients in the future.

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