Echocardiographic Evidence of Cardiac Atrophy in the Critically Ill

OBJECTIVES: The purpose of this explorative study is to determine if critically ill patients experience cardiac atrophy that can be quantified as a loss of left ventricular mass (LVM) and thus detected by echocardiography.

DESIGN: Retrospective single-center cohort study.

SETTING: Patients admitted to a tertiary medical center in Boston, MA.

PATIENTS: Adult critically ill patients with ICU length of stay greater than or equal to 5 days.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We conducted a retrospective cohort study of 68 patients, of which 42 were included in the final analysis (mean age 60.9 ± 19.2 yr; 47.6% male). The median length of ICU stay was 11.3 days (interquartile range, 6.8–20.1 d). A decrease in mean LVM over the course of admission for critical illness was observed (median 189.11 g [162.82–240.20 g] vs 176.69 g [142.37–226.26 g]; p = 0.01). After adjusting for sex, age, fluid balance, ICU type, dietary orders, time between echocardiograms, and vasopressor use, this decrease in LVM remained consistent (mean difference, –21.30 g; 95% CI, –41.85 to –0.74; p = 0.04). Relative wall thickness (RWT) did not change during admission.

CONCLUSIONS: These data reveal that a loss of LVM is present in patients over their ICU stay without a corresponding change in RWT, consistent with cardiac atrophy. Future prospective studies are needed to confirm these findings and identify possible sequelae of this finding.

KEY WORDS: critical care; critical illness; echocardiography; muscle atrophy; muscle weakness

Critical illness and the associated catabolic state are well described and consist of a constellation of signs and symptoms including weight loss, sarcopenia, and associated weakness (1). The long-term outcome for these patients is associated with worse outcomes as compared with noncatabolic counterparts, with increases in-hospital stay, mortality, time to independence, and return to work (2, 3). While prior work has demonstrated that survivors of critical illness can suffer from rapid skeletal muscle wasting, which is, in turn, a significant contributor to functional disability and poor health-related quality of life (4), there has been surprisingly little study into whether cardiac muscle is subject to similar changes. A similar loss in myocardial mass could signal disease severity and inform prognosis with far-reaching implications for the clinical management of patients.

Left ventricular mass (LVM) is the weight of the myocardium that comprises the left ventricle and is typically assessed by autopsy, estimated by cardiac MRI or echocardiography (5, 6). In general, the principle for estimation of muscle mass, regardless of technique, is based on volume calculations for common geometric shapes (5, 7). Relative wall thickness (RWT) is another parameter that can be...
determined by echocardiography and helps to categorize ventricular morphology and remodeling. The use of noninvasive imaging techniques such as echocardiography, which is an easily accessible point-of-care modality, has been validated (8) and well described (5) making it a modality that is more appealing than cardiac MRI. Interval changes have been documented in a wide spectrum of physiologic and pathologic states (9–12).

Echocardiographic quantification of LVM has been used clinically as a marker of response anti-hypertensive therapy and as a predictor of outcomes such as sudden cardiac death and arrhythmia (12–14). Changes in the echocardiographic estimates of LVM, when followed continuously, have also been predictive of mortality (14), highlighting that this parameter has both research and clinical utility. LVM may have the potential to be a clinical marker of critical illness as well as a predictor of future functional disability, morbidity, and mortality in this patient population.

To date, echocardiographic changes in LVM have not been investigated in critically ill patients. Given this gap, this study is the first exploratory study of its kind and aimed to quantify potential changes in LVM in the critically ill on echocardiography.

**MATERIALS AND METHODS**

Following approval from Committee on Clinical Investigations/Institutional Review Board (CCI/IRB) at Beth Israel Deaconess Medical Center on December 6, 2016 (Protocol number 2016P000407), patients admitted to a single, tertiary care center between September 2016 and February 2017 were screened for inclusion in this retrospective cohort study. A waiver of informed consent was obtained given the passive nature of data collection from the electronic health record. Procedures were followed in accordance with the ethical standards of the CCI/IRB and with the Helsinki Declaration of 1975.

Adult patients 18 years old or older, who were admitted to any of the six ICUs at Beth Israel Deaconess Medical Center Boston, MA, were considered eligible. Patients were included in the study if their hospital stay included an ICU admission greater than 5 days and they had at least two consecutive echocardiograms performed during that admission with the initial echocardiogram performed within one calendar day of admission to the ICU. Echocardiograms were obtained by the care team as part of routine clinical care. Within the collection period, all patients that met criteria for interval echocardiographic assessment while admitted to the ICUs were consecutively assessed.

**Echocardiographic Measurements**

Echocardiograms performed as part of routine clinical care more than 2 days apart were analyzed. All exams were performed by a licensed echocardiographer and the images were read and reported by a board-certified cardiologist in the electronic health record. Reported values documented on the official cardiology echocardiographic report were used when available. When required, measurements for calculating LVM were missing, echocardiography board-certified anesthesiologists made the appropriate measurements using the original echocardiographic images and Echo PAC software (GE Healthcare, Chicago, IL).

Measurements were made in M-mode as recommended in the American Society of Echocardiography Guidelines for Chamber Quantification (15) and verified by two members of the study team at different timepoints. Left ventricular (LV) mass and RWT were calculated using a recommended algorithm (16, 17). LVM was calculated using the following equation: $0.8 \times (1.04 \times ([LVEDD + IVSd + PWd] - LVEDD^3)) - 0.6$, where LVEDD, IVSd, and PWd represent LV, interventricular septal, and posterior wall thickness in diastole (5). RWT was calculated using the following equation: $2 \times (PWd)/LVEDD$, where PWd represents posterior...
wall thickness and LVEDD represents LV diameter in end-diastole (18).

**Data Collection**

Our primary endpoint is the change in LVM. Additional variables were abstracted from the electronic medical record and included age, gender, weight, mean arterial pressure, fluid balance, vasopressor use, beta-blocker, statin, use of neuromuscular blocking agent, diet at the time of echocardiograms, type of ICU (surgical vs medical), ICU length of stay (LOS) in days, hospital LOS in days, and ICU and hospital mortality.

**Statistical Analysis**

As there is no prior study in this space and no data published on this topic, a power calculation could not be performed. Instead, a convenience sample size of 68 consecutive patients were screened for inclusion in this explorative study.

Descriptive statistics of the data are reported as mean ± sd, median (interquartile range) or frequency counts and proportions depending on variable type (i.e., continuous or categorical) and distribution. Normality of continuous data was assessed with the Shapiro-Wilk test and confirmed with a visual inspection of the distribution. The primary outcome was LVM index, assessed as a continuously scaled value. Secondary outcomes included other echocardiographic indices including RWT.

Crude differences between the first and second echo are presented using a paired t test (for data following a gaussian distribution) or Wilcoxon signed-rank test. To assess this association after adjusting for clinically relevant covariates that were potentially confounding the association, univariate and multivariable linear mixed-effects models were employed, including a random intercept for each subject. Models were adjusted for clinically relevant covariates that were hypothesized to confound the association with LVM index. This included sex, vasopressor use at the time of the echo (binary variable), age at ICU admission, time between echocardiograms, ICU type, ICU net fluid balance, and diet at the time of the echo. Results are presented as a mean difference and its associated 95% CI. All two-sided p values of less than 0.05 were considered statistically significant. SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses.

**RESULTS**

Of the 68 patients screened for our study, 42 met inclusion criteria and were included in the final analysis (Fig. 1). The mean age of included patients was 61 ± 19 years, including 47.6% male subjects. Patients had a wide range of comorbidities as well as reasons for admission based on their admitting diagnosis (Table 1). The median ICU LOS was 11.3 days (6.8–20.1 d), with patients most commonly admitted to a cardiac care (26.2%) or cardiovascular (23.8%) ICU, followed by a medical ICU (21.4%; Table 2).

The median number of days between echocardiograms was 11.6 (5.9–18.9). Consistent with the inclusion criteria, the first echo was performed a median of 0.6 days (–0.2 to 1.2 d) from admission to the ICU. At the time of the first echocardiogram, 27 patients (64.3%) were nil per os (NPO) (Table 3). During
admission, patients were NPO for a median 130 hours (41–197 hr). A total of 36 patients (85.7%) were intubated during their ICU admission and ventilated for a median 5.1 days (1.1–11.3 d). In addition, 33 patients (78.6%) received vasopressors for a median of 1.4 days (0.6–6.7 d) (Table 2).

When evaluating changes over the course of ICU admission, a decrease in LVM was observed between the first and second echocardiogram (Fig. 2) (189.11 g [162.82–240.20 g] vs 176.69 g [142.37–226.26 g]; Table 4). Contrarily, RWT did not change over the course of admission (Table 4).

### TABLE 1. Characteristics of Enrolled Patients

| Characteristics                  | Entire Cohort, n = 42 |
|----------------------------------|-----------------------|
| Age, yr                          | 60.9 ± 19.2           |
| Male sex                         | 20 (47.62)            |
| Weight, kg                       | 77.40 (61.05–94.45)   |
| Height, cm                       | 166.9 ± 11.7          |
| Body mass index, kg/m²           | 26.29 (24.27–33.10)   |

**Comorbidities**

None 7 (16.77)
Myocardial infarction 13 (30.95)
Congestive heart failure 13 (30.95)
Cerebrovascular disease 3 (7.14)
Chronic pulmonary disease 5 (11.90)
Connective tissue disease 3 (7.14)
Mild liver disease 1 (2.38)
Moderate/severe liver disease 9 (21.43)
Diabetes without end-organ damage 1 (2.38)
Hemiplegia 7 (16.77)
Moderate/severe renal disease 2 (4.76)
Diabetes with end-organ damage 4 (9.52)
Tumor without metastasis 1 (2.38)
Lymphoma 3 (7.14)

**Diagnosis**

Cardiac 22 (52.38)
Diffuse diseases of connective tissue 1 (2.38)
Excision of esophagus 1 (2.38)
Fall 4 (9.52)
Intracranial hemorrhage 3 (7.14)
Liver disease 2 (4.76)
Necrotizing fasciitis 2 (4.76)
Renal failure 1 (2.38)
Respiratory failure 3 (7.14)
Unknown 3 (7.14)

Data are presented as n (%), mean ± sd, or median (quartile 1–quartile 3) depending on variable type and distribution.

### TABLE 2. ICU Characteristics

| Patient Characteristics                  | Entire Cohort, n = 42 |
|------------------------------------------|-----------------------|
| Weight at ICU discharge, kg              | 72.75 (58.35–89.80)   |
| Hospital length of stay, d               | 21.5 (15.0–37.0)      |
| ICU length of stay, d                    | 11.3 (6.8–20.1)       |
| Intubated during ICU stay                | 36 (85.7)             |
| Length of ventilation, d                 | 5.12 (1.11–11.29)     |

**ICU type**

Cardiovascular 10 (23.8)
Medical 9 (21.4)
Surgical 1 (2.4)
Trauma 4 (9.5)
Medical/surgical 5 (11.9)
Neuro 2 (4.8)
Cardiac care 11 (26.2)

Time nil per os during ICU admission, hr 130 (41–197)

Received during ICU stay

Statin(s) 22 (52.38)
Beta-blocker(s) 26 (61.90)
Vasopressor(s) 33 (78.57)
Time on vasopressors, d 1.42 (0.63–6.73)
Vasopressor type

Phenylephrine 18 (54.6)
Norepinephrine 27 (81.8)
Epinephrine 8 (24.2)
Vasopressin 15 (45.5)
Dopamine 3 (9.1)
Dobutamine 1 (3.0)
Neuromuscular blockade 6 (14.3)
Physicaltherapy order 35 (83.8)

ICU fluid balance, mL 1,456.62 ± 10,606.25

Data are presented as n (%), mean ± sd, or median (quartile 1–quartile 3) depending on variable type and distribution.
In univariate analyses, the difference in LVM corresponded to a 19.84 g (95% CI, –36.20 to –3.49 g; \( p = 0.02 \)) decrease between echocardiograms. When adjusted for differences in sex, age, fluid balance, ICU type, diet, time between echocardiograms, and vasopressor use, the mean decrease in LV mass remained statistically significant (–21.30 g; 95% CI, –41.85 to –0.74 g; \( p = 0.04 \); Table 4).

**DISCUSSION**

This study demonstrates a statistically significant decrease in LVM measured with echocardiography longitudinally over the course of ICU admission. These observations remained consistent between unadjusted and adjusted models. Of note, our study suggests the decrease in LVM is driven by muscle loss and not cardiac remodeling since no significant change in RWT was noted. To our knowledge, this has not been reported previously in the critical care population.

Our results demonstrate a variation of responses to critical illness. Some patients have a perceived gain in LVM, while others have a profound loss. Given the retrospective nature of this study, we were not able to determine causation. We believe this is possibly evidence of a wide array of responses various groups of patients may have to being critically ill, future studies may help to elucidate a cause for the variation in muscle mass. Overall, the cohort appeared to suffer from cardiac atrophy.

The decrease in LVM remained statistically significant when adjusted for various variables including sex, vasopressor use, age, time between echocardiograms, and fluid balance. Models were adjusted for these a priori chosen variables given their influence on baseline measurements of mass as well as their potential to drive changes or alterations in calculated or measured values (19–21). In addition to myocardial edema, fluid balance would directly affect loading conditions and cause changes in ventricular diameter, which may also lead to variations in LVM calculations. The patient sample included in this study did maintain a significant positive fluid balance during their ICU stay, but according to the model, this did not appear to have an influence on our conclusions for LV differences. Some patients in the ICU were receiving statins and beta-blockers during their critical illness but these were not significantly different between the two echocardiograms.

### TABLE 3.

**Characteristics at the Time of the Echocardiogram**

| Characteristic | Echocardiogram 1, \( n = 42 \) | Echocardiogram 2, \( n = 42 \) | \( p \) |
|---------------|---------------------------------|---------------------------------|------|
| Time from ICU admission, d | 0.62 (–0.19 to 1.17) | 11.72 (7.67–24.08) | < 0.0001 |
| Time between echocardiograms, d | – | 11.59 (5.93–18.87) | – |
| Heart rate, beats/min | 87 (70–101) | 86 (76–106) | 0.88 |
| Mean arterial blood pressure | 84 (75–90) | 79 (73–88) | 0.72 |
| Received at time of the echocardiogram | | | |
| Statin | 11 (26.2) | 17 (41.5) | 0.06 |
| Beta-blocker | 5 (11.9) | 17 (41.5) | 0.003 |
| Neuromuscular blocker | 3 (7.1) | 2 (4.9) | 0.56 |
| Vasopressor | 13 (30.9) | 9 (21.9) | 0.26 |
| Diet at the time of the echocardiogram | | | 0.15 |
| Nil per os | 27 (64.3) | 9 (21.9) | |
| Small sips of water | 1 (2.4) | 0 (0) | |
| Regular | 8 (19.1) | 19 (46.3) | |
| Tube feeds | 5 (11.9) | 12 (29.3) | |
| Total parenteral nutrition | 1 (2.4) | 1 (2.4) | |

Data are presented as \( n \) (%), mean ± so, or median (quartile 1–quartile 3) depending on variable type and distribution. Dashes indicate that value is nonsensical and cannot be calculated.
Neuromuscular blockade use was also not significantly different at these two time points. As mentioned earlier, RWT helps to define ventricular morphology and remodeling. It is a ratio of the posterior wall diameter to the LV chamber dimension in diastole multiplied by a constant. Quantification of RWT has been established in prior literature as differentiating between concentric and eccentric remodeling (18, 22). The lack of a statistically significant change in RWT in this patient sample is an important finding with implications for mechanism and potential intervention. This is consistent with the hypothesis that loss of LV mass is driven by cardiac myocyte atrophy and not cardiac remodeling with associated changes in chamber size (23). This is also in keeping with other forms of catabolic states and is an important finding, particularly in the critically ill population, given the wide variety of loading conditions seen in critically ill patients due to both pathologic and iatrogenic causes.

Additionally, no loss of significance was observed with adjustment for time between echocardiograms, vasopressor use, or diet. Since it was anticipated that nutritional status would impact cardiac muscle mass, our study findings did not show that diet type influenced myocardial mass though this may merely be due to the small sample size or that the granularity of the data was not available. Quantification of daily caloric intake may have been more informative and shown an association with LV atrophy where diet order did not. With regards to the time frame within which we see results, no data exists on the time to detect cardiac atrophy. Data for skeletal muscle atrophy in critical illness reveals that an apparent loss can be detected as early as 3 days with a significant loss at 7 and 10 days (4).

**TABLE 4. Echo Characteristics and Models**

**Echocardiogram Characteristics**

| Measurement | Echo 1, n = 42 | Echo 2, n = 42 | p |
|-------------|---------------|---------------|---|
| LVEDd (cm)  | 4.95 ± 0.81   | 4.80 ± 0.82   | 0.13 |
| LVSW (cm)   | 1.10 (1.00–1.20) | 1.00 (0.90–1.20) | 0.15 |
| LVPW (cm)   | 1.10 (1.00–1.20) | 1.00 (0.90–1.20) | 0.06 |
| RWT         | 0.46 (0.40–0.51) | 0.42 (0.38–0.50) | 0.48 |
| LVmass (g)  | 189.11 (162.82–240.20) | 176.69 (142.37–226.26) | 0.01 |

Data are presented as n (%), mean ± sd, or median (quartile 1–quartile 3) depending on variable type and distribution.

**Echocardiogram Models**

**Univariate Model**

| Measurement | Mean Difference (95% CI) | p |
|-------------|--------------------------|---|
| LVmass (g)  | −19.84 (−36.20 to −3.49) | 0.02 |
| LVEDd (cm)  | −0.16 (−0.36 to 0.05) | 0.13 |
| LVSW (cm)   | −0.04 (−0.09 to 0.02) | 0.19 |
| LVPW (cm)   | −0.04 (−0.09 to 0.02) | 0.18 |
| RWT         | 0.00 (−0.04 to 0.04) | 0.94 |

**Multivariable Model**

| Measurement | Mean Difference (95% CI) | p |
|-------------|--------------------------|---|
| LVmass (g)  | −21.16 (−41.87 to −0.46) | 0.045 |
| LVEDd (cm)  | −0.20 (−0.46 to 0.07) | 0.14 |
| LVSW (cm)   | −0.02 (−0.10 to 0.05) | 0.54 |
| LVPW (cm)   | −0.03 (−0.10 to 0.03) | 0.32 |
| RWT         | 0.00 (−0.05 to 0.05) | 0.87 |

LV = left ventricular, LVEDd = left ventricular end-diastolic diameter in diastole, LVPW = left ventricular posterior wall thickness in diastole, LVSW = left ventricular interventricular septal thickness in diastole, RWT = relative wall thickness.

*Models are adjusted for sex, vasopressor use at the time of the echo (binary variable), age at ICU admission, time between echos, ICU type, ICU fluid balance, and diet at the time of each echo.
The results of this retrospective study are analogous to those from observational studies done in different patient populations including patients with anorexia nervosa, cancer, and high endurance athletes (9, 10, 24, 25). A recent meta-analysis in anorexia nervosa revealed a standardized mean difference of 1.82 g (1.32–2.31 g; \( p = 0.001 \)) across 14 studies (26). Similarly, a recent prospective trial on patients suffering from nonsmall cell lung cancer revealed an 8.9% loss of LVM by echocardiography (27). While these represent clinically different populations, the pathophysiology of these disease states may have some commonalities with critical illness, providing a rationale for the existing data to fall within a similar range.

This study has several limitations. This is a single-center study conducted over a relatively short time period reflecting a small local patient population, thus limiting its generalizability. Given the pathophysiologic and clinical heterogeneity in critical illness and this cohort, these findings may not be true of all critically ill patients. Further, the small sample size limits the ability to further delineate findings by critical care diagnoses—for example, it is possible one could expect different findings in patients with acute exacerbation of chronic diseases as opposed to those with a traumatic injury necessitating ICU admission. We have chosen to group the patients by their admitting ICU type in order to provide an interpretable grouping of the various possible diagnoses. Additionally, in the absence of a control group, causality of cardiac atrophy cannot be attributed to critical illness. Finally, given the retrospective nature of this study, data with respect to biomarkers and other diagnoses of interest such as sepsis were not accessible at the time of analysis. The impact of these factors could be further delineated with a prospective study. These limitations are those expected from retrospective work and given that this is the first investigation in this space, these findings are hypothesis generating and provides a foundation for future work.

Echocardiographic estimates of LVM have their own set of limitations. Measurements are highly dependent on image quality and echocardiographer technique. In addition, multiple guidelines exist for defining myocardial borders and measurements and in conjunction, several methods can be used for both 2D and 3D imaging. In the present study, the Devereux equation was employed to estimate LVM, as it is both an accepted and validated method (5). Although echocardiographic estimations of LVM have some limitations, the accessibility of this technology and its growing use at the bedside outweighs these drawbacks. Future work including prospective longitudinal studies utilizing cardiac magnetic resonance, echocardiographic techniques, and biomarkers will help elucidate the usefulness of this finding for prognostication and potential interventions.

This study is the first to demonstrate changes in LVM in the critically ill population. The resultant body of work following our study has the potential to impact clinical care in the ICUs. These findings should be replicated by prospective studies as the discovery...
of cardiac atrophy in critically ill patients may offer prognostic guidance. The clinical implications of loss of cardiac muscle mass remain unknown and once identified, may offer both prophylactic and therapeutic targets in patients in the ICU. Future exploration of the clinical impact of LVM changes inspired by this novel study may further our understanding of the systemic effects of critical illness.

CONCLUSIONS

Our data reveal that a loss of LVM is present in patients over their ICU stay without a corresponding change in RWT, consistent with cardiac atrophy. Future prospective studies are needed to confirm these findings and identify future areas of study.

The authors have disclosed that they do not have any potential conflicts of interest.

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