Results from an enhanced recovery program for cardiac surgery

Michael C. Grant, MD,a,b Tetsuro Isada, MD,a Pavel Ruzankin, PhD,c,d Glenn Whitman, MD,e Jennifer S. Lawton, MD,e Jeffrey Dodd-o, MD,a and Viachaslau Barodka, MD,a Johns Hopkins Enhanced Recovery Program for the Cardiac Surgery Working Group,a,b,c,d,e,f,g,h

ABSTRACT

Objective: Enhanced recovery programs are multidisciplinary perioperative bundles of evidence-based process measures. Following the design and implementation of preanesthesia and intraoperative enhanced recovery programs for cardiac surgery guidelines, we evaluated the association between compliance and key clinical outcomes.

Methods: Consecutive patients undergoing cardiac surgery at a single tertiary medical center from September 2017 to June 2018 were included. Patients were stratified into low (0-4 measures) and high (5-7 measures) compliance groups and then 1-to-3 propensity matched on the basis of 15 patient and surgical covariables. The primary outcome of interest was time to postoperative extubation. Secondary outcomes included interval time point extubation rates and intensive care unit, floor, and hospital lengths of stay.

Results: A total of 451 patients were included in the study. After propensity matching (n = 315), patients in the high compliance group (n = 84) had a significant reduction in time to extubation (P < 0.001), floor length of stay (P = 0.01), and hospital length of stay (P = 0.03) compared with patients in the low compliance group (n = 231). Patients in the high compliance group were more likely to be extubated in the operating room (odds ratio, 35.8; 95% confidence interval, 1.18-6.07; P = 0.03) compared with patients in the low compliance group (0/62 patients). High compliance was associated with a median estimated time reduction of 3.4 hours to postoperative extubation (P < 0.001) and 19.4 hours in hospital length of stay (P = 0.001), floor length of stay (P = 0.01), and 6 hours of surgery (odds ratio, 2.6; 95% confidence interval, 1.18-6.07; P < 0.02). High compliance was associated with a median estimated time reduction of 3.4 hours to postoperative extubation (P < .001) and 19.4 hours in hospital length of stay (P = .01) compared with low compliance counterparts. There were no reintubations reported among patients extubated in the operating room (0/62 patients).

Conclusions: There is value in developing phase-specific enhanced recovery programs guidelines, which improve rates of early extubation and affect the duration of stay after cardiac surgery. These results are hypothesis generating, and further prospective study is necessary to identify clinical impact of further program expansion. (J Thorac Cardiovasc Surg 2019;■:1-10)
Enhanced recovery pathways (ERPs) are multidisciplinary perioperative pathways designed to reduce surgical insult, prevent healthcare-associated conditions, and hasten patient recovery through the bundled application of evidence-based process measures.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\) Borrowing from the original colorectal version of the program, groups have now applied ERP principles to numerous additional service lines.\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) Success among these procedures has led providers to adapt ERP frameworks to cardia surgery, for which limited early examples have shown that an ERP for cardiac surgery is equal parts feasible, advisable, and potentially effective,\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\) with at least 1 recent study that reported reduced length of stay (LOS) and improved indices of patient satisfaction associated with their program.\(^14\)

ERPs have relied thus far on the theory of marginal gains, whereby results are based on the summation of incremental—and often statistically imperceptible—benefits.\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\) Therefore, researchers have been unable to formally assess the relative contribution of measures from individual phases of care (ie, preoperative, intraoperative, postoperative) to overall outcomes. Because of the designed pragmatic stepwise implementation of an institutional ERP for cardiac surgery, our group was able to assess the impact of individual phases of program deployment. We detail the conception and implementation of the preanesthesia and intraoperative care process measures, the initial phase of program deployment, and their association with clinical milestones including postoperative extubation and phase of care lengths of stay.

### MATERIALS AND METHODS

#### Institutional Enhanced Recovery Programs for Cardiac Surgery Overview

The institutional ERP for cardiac surgery is an extension of an existing pathway instituted by the cardiac surgery Clinical Communities Committee, a multidisciplinary collaboration among surgery, anesthesiology, perioperative nursing, and others. Details of the Clinical Communities initiatives have been outlined previously.\(^15\)\(^16\) The program is sponsored by the Johns Hopkins Armstrong Institute for Patient Safety and Quality, which provides administrative support, and the Cardiovascular Thoracic Comprehensive Unit-Based Safety Program, which identifies and develops unit-specific safety and quality initiatives. In July of 2017, the group developed a pragmatic stepwise implementation strategy, which involved rolling out the ERP for cardiac surgery in a phase-of-care fashion, which includes process measures specific to the following:

- **Phase 1**: preanesthesia and intraoperative;
- **Phase 2**: preoperative (time from surgical consultation to date of surgery); and
- **Phase 3**: postoperative (immediate post-surgery to hospital discharge) care settings.

This strategy was used to allow for each phase to be both championed and evaluated independently. We report the results of preanesthesia and intraoperative stages of implementation.

#### Study Overview

After the appropriate Institutional Review Board approval, the requirement for written informed consent was waived by the Institutional Review Board. From the period of September 2017 through June 2018, data were prospectively collected and analyzed for patients undergoing cardiac surgery at Johns Hopkins Hospital, an approximately 1100-bed tertiary care academic medical center. All patients undergoing coronary artery bypass grafting (CABG), aortic, mitral, tricuspid valve, or combination procedures were included in the Enhanced Recovery After Cardiac Surgery pathway. Although patients undergoing heart transplantation or left ventricular assist device, aortic, and other cardiac procedures were also included, they were excluded from study analysis. All surgeries were performed by 1 of 6 primary board-certified cardiac surgeons. During the study period, there were no changes in staffing with regard to the surgeons, anesthesiologists, or intensive care unit (ICU) physicians.

#### Preanesthesia and Intraoperative Enhanced Recovery Programs for Cardiac Surgery Guidelines

Specific process measures included within the intraoperative guidelines were developed from a combination of literature review and institutional experience, and ultimately agreed upon by cardiothoracic anesthesiologists, surgeons, and perfusionists. These guidelines consisted of patient care process measures used throughout the preanesthesia and intraoperative phases of care (Figure E1). Patients enrolled as part of the ERP initiative were intended to receive all pathway measures unless contraindicated based on existing medical comorbidities. The decision to withhold or alter a specific intervention was guided by both the pathway outline (ie, recommended medication dose modification based on glomerular filtration rate) and individual anesthesiologist discretion. Process measure compliance rates, along with relevant patient-specific variables such as age, gender, procedure, Society of Thoracic Surgeons (STS) score, left ventricular ejection fraction, laboratory data, cardiopulmonary bypass (CPB) time, and outcomes of interest, were collected and analyzed.

#### Outcome Variables

Primary outcomes for each phase of program implementation were selected on the basis of their relationship to that specific phase of care as supported by the available literature. The primary outcome for this phase was time to endotracheal extubation after completion of surgery. This endpoint was selected because early extubation is highlighted as an STS marker for quality and has been previously used as an end point for fast-track cardiac surgery protocols.\(^7\)\(^8\)\(^9\) Phase-specific secondary
outcomes included intraoperative extubation (defined as removal of the endotracheal tube at the completion of surgery before transfer of care to the ICU), early extubation (≤6 hours of mechanical ventilation after completion of surgery), interval extubation (12 and 24 hours), ICU LOS, and floor and hospital LOS. The decision to extubate patients in the operating room was made on the basis of the discretion of individual surgical and anesthesia teams at the completion of surgery. To investigate the association between process measures and outcomes, auditing of compliance data was performed and analyzed on the following 7 interventions:

1. Acetaminophen (ie, 1000 mg; administered orally in preanesthesia area or via intravenous route in the operating room).
2. Gabapentin (ie, administered orally in the preanesthesia area; 600 mg standard dose, reduced to 300 mg if age >70 years or if renal clearance <60 mL/min).
3. Ketamine (ie, intraoperative infusion; 0.25 mg/kg/h).
4. Dexmedetomidine (ie, intraoperative infusion; 0.2-0.7 μg/kg/h; administered at the time of cardiopulmonary bypass and throughout transport to the ICU and titrated on the basis of hemodynamic and sedation goals).
5. Regional nerve block (ie, serratus anterior plane block; administered at the end of surgery under ultrasound guidance via “single-shot” technique; bupivacaine 0.25%-0.375%, 20-30 mL bilaterally).
6. Protective lung ventilation (ie, tidal volumes 6-8 mL/kg predicted body weight, positive end-expiratory pressure ≥5 cm water, Fio₂ <100%).
7. Full paralytic reversal (ie, intraoperative, administration of combination neostigmine/glycopyrrolate, or sugammadex).

These 7 process measures were chosen because (1) each measure may be reasonably hypothesized to impact the primary outcome of interest, and (2) they were uniformly adopted into practice as part of the ERP. For example, our group did not study preexisting process measures such as the use of a continuous antibiotic infusion or goal-directed perfusion protocol because these had been introduced through quality improvement initiatives before ERP deployment.

Data Collection and Statistical Analysis

Data were obtained by querying the existing institutional information system (Epic Systems Corporation, Verona, Wis). All relevant data for each patient were combined into a single patient database. Patients were categorized into high (5-7 total process measures administered per encounter) and low (0-4 measures) compliance groups to determine if overall process measure compliance was associated with selected outcomes. This cutoff was selected on the basis of a preliminary receiver operator characteristic curve, which suggested this represented the point of greatest inflection in sensitivity specificity to predict extubation within 6 hours of surgery (Figure E2). Initial univariable and subsequent multivariable logistic regression models were developed for primary outcomes in a stepwise fashion while adjusting for key covariates and independent associations were identified and reported. High compliance patients were 1-to-3 propensity matched to low compliance patients (control), and the score was estimated with logistic regression based on 15 patient-level variables to control for relevant patient and surgical covariates (Figure E3). Matching was performed for the following procedures only: CABG, aortic valve replacement, mitral valve replacement, and CABS + aortic valve replacement because of the small number of operations that incorporated other procedure types. Matching was greedy without replacement with caliper width 0.0245. Covariates’ balance was assessed in R with Cobalt package v. 3.4.1 (N. Greifer). Standardized mean differences were calculated with pooled variances. The adjustment validation requirement included absolute standardized mean differences less than 0.1 and variance ratios less than 2 for all the covariates. The Love Plot depicting the covariates’ balance is shown in Figure E3. Overall all results are expressed in unmatched and matched forms. For continuous variables, data are expressed as mean value ± standard deviation. For unmatched binary variables, data are expressed as count (percentage). Finally, for matched binary variables, data are expressed as weighted count (percentage) (unweighted count [percentage]). Comparisons are analyzed by Mann–Whitney or Fisher exact test where appropriate. Kaplan–Meier plots for each outcome are analyzed using the log-rank test. To estimate the median time reduction to extubation and in LOS, we used a censored quantile regression doubly robust model (ie, censored quantile regression was run for weighted matched observations with the same covariates as for propensity score estimation). Median difference was expressed as time difference in hours with 95% confidence interval (CI). Data were processed and analyzed with the software programs Excel, v. 14.0 (Microsoft Inc, Redmond, Wash), Stata v.14.2 (StataCorp, LP, College Station, Tex), and R v. 3.5.0 (R Core Team) statistical packages.

RESULTS

Study Population and Demographics

In total, 451 consecutive patients were included in our cohort, with patient characteristics represented in Table 1. Among unmatched patients, the high compliance group was represented by patients with lower STS scores (1.38 vs 2.45%; P < .001) and shorter CPB time (100.7 vs 121.3 minutes; P = .002) compared with the low compliance group. Overall procedure breakdown is also remarkable for fewer combination procedures in the high compliance group (4.8% vs 15.3%; P = .04) as well. After propensity score matching, there were 315 patients (n = 231 and 84 in the low and high compliance groups, respectively).

Process Measure Compliance and Time to Postoperative Extubation

The association between process measure compliance and time to extubation is shown in Figure 1. Overall, high compliance was associated with earlier postoperative extubation compared with low compliance counterparts (Figure 1, A: unmatched; Figure 1, B: matched; P < .001 for each, respectively). Within the matched cohort, high compliance patients were significantly more likely to be extubated in the operating room (Table E1; odds ratio, 35.8; CI, 10.7-168.8; P < .001) compared with low compliance patients, with 47.6% of high and 4.8% of low compliance patients extubated at the time of surgical completion. Within the matched cohort, high compliance patients were also more likely to be extubated at 6 hours (odds ratio, 2.6; 95% CI, 1.18-6.07; P < .02) compared with low compliance patients. The overall rate of reintubation was 5.3% (unmatched data; 24/451), with 5.8% (20 of 347) in the low compliance group and 3.8% (4 of 104) in the high compliance group. Among patients who were extubated intraoperatively (46 in the high and 16 in the low compliance group), there were no subsequent reintubations. Figure 2 depicts the patient-specific individual and composite process measure compliance over the duration of the study. As shown, compliance improved throughout the study period, with the final individual and
TABLE 1. Patient cohort demographics stratified according to process measure compliance and propensity-matching statistics

<table>
<thead>
<tr>
<th></th>
<th>Unmatched</th>
<th>Matched</th>
<th>Absolute standardized mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All cases</td>
<td>0-4 process measures</td>
<td>5-7 process measures</td>
</tr>
<tr>
<td>Cases, No.</td>
<td>451 (100.0%)</td>
<td>347 (100.0%)</td>
<td>104 (100.0%)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>332 (73.6%)</td>
<td>249 (71.8%)</td>
<td>83 (79.8%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>63.8 (±11.8)</td>
<td>64.2 (±11.9)</td>
<td>62.6 (±11.6)</td>
</tr>
<tr>
<td>STS score, %</td>
<td>2.21 (±3.48)</td>
<td>2.45 (±3.74)</td>
<td>1.38 (±2.26)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>53.30 (±12.13)</td>
<td>52.75 (±12.46)</td>
<td>55.14 (±10.78)</td>
</tr>
<tr>
<td>Preoperative hemoglobin, g/dL</td>
<td>12.97 (±2.16)</td>
<td>12.96 (±2.21)</td>
<td>12.98 (±1.98)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.22 (±1.09)</td>
<td>1.23 (±1.18)</td>
<td>1.17 (±0.72)</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0.98 (±0.49)</td>
<td>0.98 (±0.52)</td>
<td>0.96 (±0.38)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.69 (±20.45)</td>
<td>86.88 (±21.66)</td>
<td>86.04 (±15.83)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.72 (±0.10)</td>
<td>1.72 (±0.10)</td>
<td>1.73 (±0.09)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.01 (±0.26)</td>
<td>2.01 (±0.27)</td>
<td>2.01 (±0.21)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>116.5 (±53.8)</td>
<td>121.3 (±57.0)</td>
<td>100.7 (±37.3)</td>
</tr>
<tr>
<td>CABG</td>
<td>303 (67.2%)</td>
<td>225 (64.8%)</td>
<td>78 (75.0%)</td>
</tr>
<tr>
<td>AVR</td>
<td>42 (9.3%)</td>
<td>31 (8.9%)</td>
<td>11 (10.6%)</td>
</tr>
<tr>
<td>MVR</td>
<td>41 (9.1%)</td>
<td>34 (9.8%)</td>
<td>7 (6.7%)</td>
</tr>
<tr>
<td>CABG + AVR</td>
<td>36 (8.0%)</td>
<td>32 (9.2%)</td>
<td>4 (3.8%)</td>
</tr>
<tr>
<td>CABG + MVR</td>
<td>9 (2.0%)</td>
<td>9 (2.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AVR + TVR</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AVR + MVR + TVR</td>
<td>2 (0.4%)</td>
<td>2 (0.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AVR + MVR</td>
<td>6 (1.3%)</td>
<td>6 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>TVR</td>
<td>7 (1.6%)</td>
<td>4 (1.2%)</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>AVR + MVR + CABG</td>
<td>2 (0.4%)</td>
<td>1 (0.3%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>MVR + TVR</td>
<td>2 (0.4%)</td>
<td>2 (0.6%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Data expressed as mean value ± standard deviation. STS, Society of Thoracic Surgeons; BSA, body surface area; CABG, coronary artery bypass grafting; AVR, aortic valve replacement/repair; MVR, mitral valve replacement/repair; TVR, tricuspid valve replacement/repair. *STS score in unmatched data is the composite of CABG, AVR, MVR, and combination thereof procedures.

Composite compliance reaching greater than 70%. The Figure 3 depicts the percentage of patients who received a certain number of process measures over the duration of the study. As compliance increased, so did the percentage of patients who were extubated in the operating room as well as within 6 hours of surgery.

Multivariable regression analysis revealed that lower STS risk score ($P = .002$) and shorter CPB time ($P < .001$) were independently associated with extubation 6 hours or less. Whereas reversal of paralysis ($P < .001$), use of gabapentin ($P = .003$), regional analgesia ($P = .01$), and dexmedetomidine ($P = .02$) were independently associated with intraoperative extubation, only reversal of paralytic in the operating room was also independently associated with extubation 6 hours or less ($P < .001$; Table E2).

Process Measure Compliance and Intensive Care Unit Length of Stay

The association between process measure compliance and ICU LOS in hours is shown in Figure E4. Although high compliance was associated with a shorter LOS compared with low compliance counterparts among unmatched results (Figure E4, A; $P = .01$), there was no difference in ICU LOS between groups in the propensity-matched cohort (Figure E4, B; $P = .66$).

Process Measure Compliance and Floor Length of Stay

The association between process measure compliance and floor LOS in hours is shown in Figure E5. High compliance was associated with a significantly shorter floor LOS.
(difference between floor LOS and ICU LOS) compared with low compliance among unmatched (Figure E5, A; \( P < .001 \)) and propensity-matched (Figure E5, B; \( P = .01 \)) cohorts.

**Process Measure Compliance and Hospital Length of Stay**

The association between process measure compliance and hospital LOS in hours is shown in Figure 4. High compliance was associated with a significantly shorter length of hospital stay compared with low compliance patients among unadjusted (Figure 4, A; \( P < .001 \)) and propensity-matched (Figure 4, B; \( P = .03 \)) cohorts.

**Median Time Reduction Analysis**

Results of the doubly robust censored quantile regression analysis are expressed in Table 2. As shown, high compliance patients have a shorter time to extubation (propensity
matched; 0.5 vs 5 hours) compared with low compliance counterparts, resulting in a median estimated time reduction of 3.4 hours ($P < .001$). High compliance patients also have a shorter floor (98.5 vs 119 hours) and hospital (142 vs 163 hours) LOS compared with low compliance patients with a median estimated time reduction of 20.5 hours ($P = .006$) and 19.4 hours ($P = .01$), respectively.

**DISCUSSION**

Compliance with preanesthesia and intraoperative process measures is associated with earlier rates of postoperative extubation, a statistically significant effect noted at the intraoperative and 6-hour time points. Although it does not affect ICU LOS, compliance is associated with a significant reduction in floor and overall hospital LOS, with the high compliance cohort experiencing a median reduction in hospital LOS of approximately 20 hours compared with low compliance counterparts. These findings suggest that interventions isolated to the preanesthesia and intraoperative setting may provide value throughout the duration of the cardiac surgical encounter. To our knowledge, this represents the first evaluation of a phased implementation
strategy and assessment of the impact of process measure compliance on clinical outcomes in an ERP for cardiac surgery. An overview of the study and key results are provided in Video 1.

The selected interventions introduced in this study are borne from existing literature that supports their use as measures to hasten recovery from anesthesia, optimize multimodal analgesia, and limit the harmful impact of mechanical ventilation. They include preventative multimodal acetaminophen, gabapentin, intraoperative ketamine infusions, and regional analgesia, which have been shown to reduce perioperative opioid administration in cardiac and other types of surgery, and therefore may reduce the impact of the anesthetic on rates of recovery. We incorporated a lung protective mechanical ventilation strategy, evidenced to reduce rates of postoperative lung injury and pneumonia. Perioperative sedation was facilitated through the use of dexmedetomidine, which is shown

![Unmatched](A)

Unmatched

![Matched](B)

Matched

FIGURE 4. Overall hospital LOS as a function of compliance with phase-specific process measures. Unmatched (A) and propensity-matched (B) cohorts. As shown, high compliance with phase of care guidelines (red; 5-7 process measures) is associated with a significant reduction in length of hospital stay compared with low compliance (blue; 0-4 process measure) counterparts.
to reduce incidence of postoperative delirium and increase the likelihood of 8-hour extubation compared with propofol.28,29 Finally, providers were encouraged to fully reverse muscle relaxation in the operating room, thereby hastening return of spontaneous ventilation and potentiate assessment for early extubation.

A great deal of prior work has been devoted to cardiac surgical pathway development, with perhaps the most noteworthy example being fast-track cardiac surgery. These pathways were designed to reduce the use of opioid-based anesthetics and hasten time to postoperative extubation.30-32 Although fast-track cardiac surgery led to shorter durations of mechanical ventilation, a recent meta-analysis determined that this did not necessarily translate into improved downstream clinical outcomes because there were similar overall LOS.19 As a result, there remains controversy regarding the true clinical impact of early extubation. A recent editorial suggested that early extubation is not only an outcome associated with the intraoperative management but also a key intermediary to subsequent care. If this were entirely true, it is unlikely that early extubation alone could account for a nearly full day of LOS reduction. Alternatively, it may be true that the multidisciplinary decision to extubate early is an independent predictor of early discharge as well—essentially that healthier patients are selected for earlier extubation. Although possible, propensity matching suggests that among similar patients, high compliance was more strongly associated with both early extubation and LOS. Most likely, our findings suggest that early extubation is both facilitated by and a marker of optimal intraoperative management. A goal-oriented intraoperative plan may allow for immediate de-escalation in organ support (ie, extubation), management that is typically reserved for the “next” phase of care (ie, reversal of paralysis, removal of sedation, weaning of vasopressors in the ICU). Subsequent pathway elements (ie, oral feeding, ambulation, and Foley and central line removal) may continue on the basis of individual patient milestones rather than discrete patient location (ie, ICU vs intermediate care unit vs surgical ward). Further, patients are optimized to tolerate subsequent care elements because of the goal-directed nature of their intraoperative care. This approach stands in contrast to prior early extubation strategies, which have underemphasized the role of the anesthesia and analgesia plan. In this study, de-escalation planning actually begins more or less at the surgical outset through the use of select anesthetics and analgesics that reduce ongoing impact beyond the completion of surgery. Extubation, although an important milestone, is less an outcome of the program and perhaps more a marker of sound intraoperative management.

<table>
<thead>
<tr>
<th>TABLE 2. Estimated median time reduction to extubation and length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmatched: Median time, h</strong></td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td><strong>0-4 process measures</strong></td>
</tr>
<tr>
<td>Extubation</td>
</tr>
<tr>
<td>Admission in ICU</td>
</tr>
<tr>
<td>Admission on floor</td>
</tr>
<tr>
<td>Admission in hospital</td>
</tr>
</tbody>
</table>

Data expressed as value in hours with 95% CIs. ICU, Intensive care unit.

VIDEO 1. Dr Michael Grant explains the design and key findings of an enhanced recovery program for cardiac surgery at Johns Hopkins University. Video available at: https://www.jtcvs.org/article/S0022-5223(19)31136-5/fulltext.
One compelling finding in this study is the significant increase in the rate of intraoperative extubation within the high compliance group. Because of the retrospective nature of our study design, we were unable to conclusively separate the impact of process measure compliance from the providers’ decision to extubate. As a result, although it is likely that intraoperative extubation in particular led to improved overall rates of early extubation, we are unable to make larger conclusions regarding the importance of intraoperative extubation overall. Certainly, intraoperative extubation is an uncommon practice in cardiac surgery and thus far generally unstudied. Therefore, it remains unclear whether intraoperative extubation is associated with superior outcomes compared with early (<6 hours) extubation, and this remains an opportunity for future prospective study. Although our findings do not suggest harm in the practice, we hesitate to promote its widespread adoption based on these limited results. Further, even in institutions where providers prefer to adhere to an initial postoperative observation period to evaluate for patient stability before extubation, the results of our study suggest that compliance with these measures are likely to facilitate improved rates of early postoperative extubation.

The ERP for cardiac surgery program highlighted several important barriers and facilitators to implementation. As shown, compliance was notably poor at the outset. Although reasons for poor compliance are speculative, they likely stem from failure to prospectively address system-level obstacles, including preanesthesia nursing workflow, formal and consistent education of staff in each phase of care, medication formulary restrictions, comfort of the intraoperative providers to administer individual process measures (ie, regional anesthesia), and consistent multidisciplinary acceptance. Mitigation strategies included, in kind, the development of electronic preanesthesia order sets and nursing education, identification of individual discipline program champions, work to gain medication approval/availability, and a continuous auditing and provider feedback process. In addition, there were intraoperative workflow delays, especially at program inception, associated with the administration of regional nerve blocks and intraoperative extubation. These were, at times, met with resistance, something that may be particularly true in high-turnover centers where these efforts are perceived as bottlenecks to efficiency. Regular communication of the ultimate program goals, development of strategies to ensure improvement in efficacy and timing of measures, and publication of local compliance/outcome data helped to reinforce support from surgery and anesthesiology.

Finally, it should be noted that whereas the ICU had previously established an early extubation algorithm, additional support and communication were necessary to potentially receive and recover an extubated patient, including adequate nursing and respiratory staff, bedside advanced providers, rescue airway specialists, and the presence of noninvasive ventilation devices (ie, high-flow nasal cannula or bilevel positive airway pressure). Recognition of existing barriers and deployment of their associated solutions that fostered program success were the product of an established culture of perioperative pathway development via multidisciplinary collaboration, top-down administrative support, and use of similar strategies to address potential patient harms in other clinical arenas.

Study Limitations
There are several important limitations to this study. Data presented are specific to a single academic institution. Interpretation and extrapolation of results should be done with caution, because they are potentially influenced by unmeasured factors such as local medication formulary, unique workforce structure, unit-level protocols/workflows, and intangibles such as service line culture. Although it is likely that foundational principles such as the establishment of a multidisciplinary team, use of evidence-based interventions, guideline development, and system auditing are transferrable, we are unable to comment on the potential impact of adoption of a similar program elsewhere. Because of pragmatic rather than randomized nature of our study, the most significant limitation is the potential for bias, because healthier patients undergoing less complex procedures are typically more likely to tolerate care elements and advance along the pathway. Therefore, it is possible that intraoperative observations by the anesthesiologist led them to deviate from the pathway guidelines. Although we attempt to mitigate for confounders such as patient or surgery-specific variables through the use of propensity score matching and multivariable regression strategies, we cannot exclude the potential for provider or selection bias. Full accounting for intraoperative surgical complications such as bleeding, hemodynamic instability, or other untoward events is not feasible. We recommend these results be viewed as hypothesis generating and recognize the importance of further discovery in this area.

CONCLUSIONS
We outlined the initial conception, design, and implementation of an institutional ERP for cardiac surgery. The results suggest that deployment and compliance with a concerted preanesthesia and intraoperative set of evidence-based guidelines may lead to early extubation and translate into shorter lengths of hospital stay after cardiac surgery. Future study is anticipated to assess the impact of greater program expansion, including preoperative and postoperative process measures, on additional clinical outcomes.
Conflict of Interest Statement
Grant is on the Executive Board of the ERAS Cardiac Society. All other authors have nothing to disclose with regard to commercial support.

References

Key Words: enhanced recovery after surgery, cardiac surgical pathways, perioperative medicine, bundled health care, quality improvement
Enhanced Recovery Program for Cardiac Surgery
Preanesthetic and Intraoperative Guidelines

Preanesthesia:
Goals: liberation of NPO status, multimodal analgesia to limit reliance upon opioids, beta blockade

- Recommend preoperative analgesic medication bundle to be taken with a sip of water in the PACU:
  - Gabapentin 600 mg PO x1
    - Do not give to patients on hemodialysis, consider holding in Stage IV chronic renal insufficiency, reduce dose to 300mg in patients >70 years of age
  

  - Acetaminophen 1 gm PO x1
    - Do not give to patients with liver failure/cirrhosis and consider reduction to 650 mg in patients with ALT/AST >10x ULN
  

  - Beta-blocker (home agent and dose) PO x1
    - For CABG patients ONLY [Cardiac SCIP/STS Measure]

Intraoperative (Prior to CPB):
Goals: multimodal analgesia to minimize opioid use, prevention of surgical site infection, tight glucose control, protective lung ventilation to avoid pulmonary complication

- Consider Midazolam at induction (or pre-treatment): 0.02-0.05 mg/kg bolus (1-5 mg) for anxiolysis, treatment of PONV and offset potential hallucination side effect of unopposed ketamine (below)
  - Recommend reducing or omitting use in elderly (age > 70) or frail patients
  

- Consider Ketamine: 0.25 mg/kg/hr infusion initiated after induction; discontinue at time of transport
  - Bolus dosing (in isolation) has been shown to be ineffective in reducing perioperative opioid use or improving pain scores; provider discretion if boluses may aide in more stable induction
  

- Recommend initiating dexmedetomidine infusion (no bolus; 0.5 – 0.7 mcg/kg/hr) prior to (just after central line placement) or during CPB. Continue throughout the case and upon admission to the ICU
  
  [Anesthesiology. 2016 Feb;124(2):362-8]

- For CABG: if patient did NOT take beta-blocker prior to surgery, please administer metoprolol IV unless the patient’s heart rate is < 50 bpm
  - If you do not give beta-blocker, please document the rationale in the electronic record

- Cefazolin 2 gm (3 gm if > 120kg) + 1 gm/hr (reduce to 0.5 g/hr if CrCl30-60 mL/min, or to 0.33 g/hr if CrCl <30 or patient receiving dialysis) infusion during surgery; stop infusion prior to transport
  - If penicillin allergic: vancomycin 15 mg/kg bolus over 1 hour prior to surgical incision
  
  [Cardiothoracic Vasc Anesth. 2015 Dec;29(5):1382-7.]

- Lung protective ventilation strategy ~ 6 mL/kg tidal volume predicted body weight + 5 cm H2O of PEEP (Reference Chart for Tidal Volumes)

FIGURE E1. The Johns Hopkins Medical Institutions preanesthesia and intraoperative ERP for cardiac surgery guidelines. NPO, Nil per os; PACU, post-anesthesia care unit; PO, per os; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; CABG, coronary artery bypass graft; hr, hour, bpm, beats per minute; PEEP, positive end expiratory pressure; FiO2, fraction of inhaled oxygen; PaO2, partial pressure of oxygen; SaO2, oxygen saturation; ABG, arterial blood gas; VBG, venous blood gas; Q1 hour, every hour; ACT, activated clotting time; FFP, fresh frozen plasma; MAP, mean arterial pressure; TEG, thromboelastography; CPB, cardiopulmonary bypass.
- Recommend FiO2 60% or less
- If PaO2 < 80 or SaO2 < 92%, perform standard recruitment on AYSIS GE machine (35 mmHg for 15 seconds) every 30 minutes unless contraindicated
- Recommend holding mechanical ventilation while on bypass; no clear strategy that definitively improves postoperative outcome


- Recommend an initial arterial and venous blood gas (ABG, VBG) + ACT at start of case
- Recommend repeating ABG + "CORE4" + lactate Q1 hour for case duration

- **Insulin** bolus + infusion as indicated based upon the protocol (Intraoperative Insulin Protocol; goal glucose < 180)

**IV fentanyl or IV hydromorphone**: Intermittent intravenous opioid at provider discretion
- AVOID ultra-short acting opioids with high incidence of medication-induced tachycardia and hypertension (i.e. remifentanil)
- AVOID long-acting opioids (i.e. methadone) given unpredictable metabolism profile and potential association with postoperative ileus

**Intraoperative (During CPB):**
**Goals**: Adequate anticoagulation, anti-fibrinolysis and cardiopulmonary perfusion

- **Heparin** 350 unit/kg bolus (ACT goal > 480); initiate heparin infusion at rate = 1/3rd of bolus dose/hr throughout cardiopulmonary bypass
  - If ACT < 480, please administer an additional 10,000 units of heparin and repeat ACT
  - If ACT is still < 480 after a total heparin dose of ≥650 units/kg, consider either lower ACT goal, administration of antithrombin III (ATIII) concentrate per protocol (ATIII Concentrate Protocol), or FFP 2-3 units (if available in the room)

- At time of heparin bolus, **tranexamic acid** 10 mg/kg bolus over 10 minutes through the Alaris pump + 1 mg/kg bolus in the CPB circuit + 1 mg/kg/hr infusion through the Alaris pump throughout the surgery


- **Goal-directed perfusion** per our institutional guidelines (Goal Directed Perfusion Protocol)
  - If perfusion utilizes > 1,000 mcg of phenylephrine and increased flow (cardiac index > 2.4; per perfusion) do not maintain MAP > 60, please initiate a **norepinephrine infusion** during CPB

**Intraoperative (During Rewarming):**
**Goals**: Goal directed transfusion, adequate warming

- Send **coagulation labs** (platelet count, fibrinogen and cardiac TEG) when aortic cross-clamp is removed; transfuse as appropriate based upon abnormalities PLUS active bleeding (Coagulation Study Protocol)

- **Goal hemoglobin transfusion trigger recommendation is 7.5**, regardless of patient age or comorbidities provided no active large volume bleeding
  - Please discuss transfusion(s) with anesthesiology, surgery and perfusion personnel at surgical timeout and again at the time of decision to transfuse


- Turn on **bear hugger** to boost and increase room temperature to 68 degrees to ensure adequate warming and assist in the prevention of coagulopathy (goal postop temperature of > 36.0 degrees)

**FIGURE E1. (continued).**
Hypothermia is a reason for failure to extubate the patient within 6 hours

**Intraoperative (After CPB Separation):**

Goals: adequate hemostasis, electrolyte repletion, multimodal analgesia to minimize opioid use and mechanical ventilator weaning

- Ensure adequate heparin reversal after protamine administration via ACT (goal ~ baseline ACT), consider repeating coagulation laboratories after factor/platelet administration

- Ensure adequate repletion of calcium (goal iCal 1.1) and potassium (goal K > 4.0) by case completion
  - Remember: epinephrine +/- insulin +/- acidosis all impact plasma K levels


- Recommend **IV acetaminophen 1000 mg x1** at 6-8 hours after initial oral preoperative administration if still in the operating room. Do **not give** if AST/ALT >10x ULN. [Thorac Cardiovasc Surg 2016;152:881-9]

- Recommend **Regional Analgesia Block:** 0.25 – 0.375% bupivacaine 20-30 mL via ultrasound guidance bilateral at the time of surgical drape removal
  - **NOTE:** If you plan to perform an this block please do NOT perform a surgical incision block due to the risk of local anesthesia toxicity

- Multidisciplinary discussion to determine if **extubation in the operating room** is appropriate. If so, paralysis should be fully reversed, weaned to pressure support, titrate analgesics and extubate trachea
  - If extubation is not desired or is inappropriate, then at the time of ICU handoff, all patients should have their **muscle paralysis fully reversed**

- Recommend the use of **dexametomidine** infusion over propofol for transportation to ICU

**FIGURE E1.** (continued).
FIGURE E2. Results of a preliminary receiver operator characteristic curve, which helped to establish the cutoff number (between 4 and 5) of measures necessary for maximal sensitivity and specificity to predict postoperative extubation within 6 hours of surgery.

FIGURE E3. The Love plot depicting the results of propensity matching. Although among unmatched data, there is a significant difference between high compliance and low compliance cohorts with respect to STS score, ejection fraction, and CPB time, there is excellent matching between groups as evidenced by an absolute standardized mean difference of less than 0.1 and variance ratio less than 2 for all 15 selected covariates. CABG, Coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; STS, Society of Thoracic Surgeons; BSA, body surface area.
FIGURE E4. ICU LOS as a function of compliance with phase-specific process measures. Unmatched (A) and propensity-matched (B) cohorts. As shown, there is no difference in ICU LOS between high (red; 5-7 process measures) and low compliance (blue; 0-4 process measure) cohorts. ICU, Intensive care unit.
FIGURE E5. Floor LOS as a function of compliance with phase-specific process measures. Unmatched (A) and propensity-matched (B) cohorts. As shown, high compliance with phase of care guidelines (red; 5-7 process measures) is associated with a significant reduction in length of floor stay compared with low compliance (blue; 0-4 process measure) counterparts.
TABLE E2. Results of multivariable regression analysis on various timeframes of extubation

<table>
<thead>
<tr>
<th>Extubation time</th>
<th>OR; 5-7 vs 0-4 process measures</th>
<th>OR; 6 h vs 0-4 process measures</th>
<th>OR; 12 h vs 0-4 process measures</th>
<th>OR; 24 h vs 0-4 process measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>35.76 (10.66, 168.75)</td>
<td>&lt; .001</td>
<td>2.62 (1.18, 6.07)</td>
<td>.02</td>
</tr>
<tr>
<td>≤ 6 h</td>
<td>1.79 (0.59, 5.90)</td>
<td>.31</td>
<td>0.72 (0.01, 8.14)</td>
<td>.79</td>
</tr>
<tr>
<td>≤ 12 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ORs were computed with logistic regression doubly robust model. OR, Odds ratio.

**TABLE E1. Odds of extubation based on compliance group**

<table>
<thead>
<tr>
<th>Extubation time</th>
<th>OR; 5-7 vs 0-4 process measures</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>35.76 (10.66, 168.75)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>≤ 6 h</td>
<td>2.62 (1.18, 6.07)</td>
<td>.02</td>
</tr>
<tr>
<td>≤ 12 h</td>
<td>1.79 (0.59, 5.90)</td>
<td>.31</td>
</tr>
<tr>
<td>&lt; 24 h</td>
<td>0.72 (0.01, 8.14)</td>
<td>.79</td>
</tr>
</tbody>
</table>

The Journal of Thoracic and Cardiovascular Surgery • Volume ■, Number ■ 10.e7

**TABLE E2. Results of multivariable regression analysis on various timeframes of extubation**

<table>
<thead>
<tr>
<th>Extubation time</th>
<th>OR; 5-7 vs 0-4 process measures</th>
<th>OR; 6 h vs 0-4 process measures</th>
<th>OR; 12 h vs 0-4 process measures</th>
<th>OR; 24 h vs 0-4 process measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>1.46 (0.60, 3.57)</td>
<td>.40</td>
<td>0.84 (0.50, 1.38)</td>
<td>.48</td>
</tr>
<tr>
<td>Paralytic reversal (operating room)</td>
<td>13.92 (5.37, 40.44)</td>
<td>&lt; .001</td>
<td>2.96 (1.59, 5.69)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Dexametomidine</td>
<td>0.33 (0.12, 0.83)</td>
<td>.023</td>
<td>0.56 (0.27, 1.16)</td>
<td>.12</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>1.94 (0.58, 6.44)</td>
<td>.27</td>
<td>1.61 (0.82, 3.28)</td>
<td>.18</td>
</tr>
<tr>
<td>Regional Analgesia</td>
<td>2.75 (1.25, 6.24)</td>
<td>.013</td>
<td>1.13 (0.62, 2.11)</td>
<td>.69</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4.73 (1.77, 14.39)</td>
<td>.003</td>
<td>1.03 (0.47, 2.20)</td>
<td>.94</td>
</tr>
<tr>
<td>Protective lung ventilation</td>
<td>1.88 (0.17, 50.56)</td>
<td>.64</td>
<td>0.34 (0.10, 1.04)</td>
<td>.072</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (1.00, 1.00)</td>
<td>.18</td>
<td>1.00 (1.00, 1.00)</td>
<td>.81</td>
</tr>
<tr>
<td>STS score</td>
<td>0.73 (0.45, 0.99)</td>
<td>.13</td>
<td>0.82 (0.72, 0.92)</td>
<td>.40</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>1.02 (0.98, 1.06)</td>
<td>.40</td>
<td>1.01 (0.99, 1.03)</td>
<td>.20</td>
</tr>
<tr>
<td>Preoperative hemoglobin</td>
<td>0.99 (0.79, 1.26)</td>
<td>.96</td>
<td>1.00 (0.87, 1.15)</td>
<td>.96</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.01 (0.52, 1.70)</td>
<td>.97</td>
<td>0.99 (0.77, 1.23)</td>
<td>.93</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.91 (0.31, 2.58)</td>
<td>.86</td>
<td>0.48 (0.25, 0.93)</td>
<td>.029</td>
</tr>
<tr>
<td>Weight</td>
<td>1.09 (0.99, 1.20)</td>
<td>.075</td>
<td>0.99 (0.94, 1.05)</td>
<td>.78</td>
</tr>
<tr>
<td>Gender</td>
<td>1.68 (0.45, 6.41)</td>
<td>.44</td>
<td>0.71 (0.33, 1.51)</td>
<td>.38</td>
</tr>
<tr>
<td>Height</td>
<td>1499.15 (0.56, &gt;2000)</td>
<td>.08</td>
<td>1.47 (0.01, 183.30)</td>
<td>.88</td>
</tr>
<tr>
<td>BSA</td>
<td>0.00 (0.00, 0.60)</td>
<td>.044</td>
<td>4.43 (0.02, 1002)</td>
<td>.59</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>1.0007 (0.99, 1.01)</td>
<td>.89</td>
<td>0.9904 (0.99, 1.01)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>AVR vs CABG</td>
<td>2.98 (0.88, 9.79)</td>
<td>.073</td>
<td>4.24 (1.58, 13.85)</td>
<td>.008</td>
</tr>
<tr>
<td>MVR vs CABG</td>
<td>6.62 (1.52, 29.35)</td>
<td>.012</td>
<td>0.84 (0.34, 2.15)</td>
<td>.71</td>
</tr>
<tr>
<td>CABG + AVR vs CABG</td>
<td>2.75 (0.47, 13.52)</td>
<td>.23</td>
<td>1.01 (0.43, 2.46)</td>
<td>.98</td>
</tr>
</tbody>
</table>

Bold values represent statistical significance based on the established threshold of < .05. OR, Odds ratio; STS, Society of Thoracic Surgeons; BSA, body surface area; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; MVR, mitral valve replacement.
Results from an enhanced recovery program for cardiac surgery
Michael C. Grant, MD, Tetsuro Isada, MD, Pavel Ruzankin, PhD, Glenn Whitman, MD, Jennifer S. Lawton, MD, Jeffrey Dodd-o, MD, and Viachaslau Barodka, MD, Johns Hopkins Enhanced Recovery Program for the Cardiac Surgery Working Group, Baltimore, Md; Novosibirsk, Russia; Houston, Tex; and Hershey, Pa

There is value in developing phase of care guidelines for ERPs for cardiac surgery, which may improve rates of early extubation and reduce LOS after cardiac surgery.