

Less Is More

A Superior Clinical Strategy?

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CME

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“LESS is more.” Increasingly, it appears that this pithy adage may be an effective clinical strategy. The past 20 yr of medical science are littered with clinical interventions that were once commonplace and of biologically plausible value, yet were found to be ineffective or harmful when long-term, patient-centered outcomes were evaluated robustly using insightful analyses. Routine pulmonary artery catheterization, widespread preoperative exercise tolerance testing, intensive insulin therapy, and active cooling during cerebrovascular procedures have all been found to be ineffective when evaluated using large-scale effectiveness trials and observational analyses. Similarly, in this issue of ANESTHESIOLOGY, Nielsen *et al.*¹ add to a growing body of literature suggesting that the routine use of inotropic therapy in cardiac surgery patients may cause more harm than good.

Using a validated clinical registry of 6,005 cardiac surgery patients across three Danish academic medical centers, the authors retrospectively compared the outcomes of patients with and without perioperative inotropic therapy consisting of milrinone, dobutamine, dopamine, epinephrine, or levosimendan. Approximately 35% of patients received one of these agents during or after cardiac surgery. As expected, many of the patients exposed to these inotropes were older, sicker, and undergoing more complex surgeries. However, due to the clinical equipoise regarding the use of inotropes during cardiac surgery, similar patients experienced wide variation in care. Using robust propensity score–matching techniques, the authors were able to create two analytical cohorts (inotropes *vs.* no inotropes) that were very similar based on measurable



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patient, procedure, anesthetic, and provider characteristics. Despite these similar underlying characteristics, patients exposed to inotropes were more prone to a wide range of in-hospital complications: 30-day mortality, renal replacement therapy, myocardial infarction, and stroke. More importantly, this effect was continued until 1 yr of follow-up, when all-cause mortality was still increased. Most striking was the level of clinical significance observed by the authors: patients exposed to inotropes were twice as likely to experience myocardial infarction, nearly four times as likely to die at 30 days, and eight times as likely to require renal replacement therapy. Of note, patients exposed to isolated intraoperative inotropes fared much better than those who received intraoperative *and* postoperative inotropes: their short-term and long-term mortality was similar to patients without any inotropes.

The conscientious and insightful clinician is left with a troubling question: should these provocative data warrant the avoidance of routine inotrope administration? The answer is complex and reveals the challenges and opportunities of robust observational analyses such as the one performed by these authors. All new scientific data must be evaluated in the context of current knowledge and the maturity of the existing literature. The prospective data establishing the value of inotropic therapy is limited to short-term hemodynamic endpoints. We have convincing data that inotropic therapy does make the patient’s objective intraoperative hemodynamic data “better.” Cardiac output is improved, although at the expense of systemic vascular resistance, mean arterial pressure, myocardial oxygen supply/demand balance,

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and cellular calcium overload. We have historically assumed that improving the cardiac output of a surgically traumatized heart is a reasonable standard of care. However, the current data combined with previous observational analyses demonstrating the risk of specific agents such as dobutamine² and milrinone³ shines a glaring light on the absence of prospective data demonstrating that increasing cardiac output *via* inotropic support improves clinical outcomes or mortality. There are no clinical outcome efficacy data supporting the use of inotropic therapy. As a result, the work by Nielsen *et al.* should affect clinical care. In the absence of prospective interventional or observational data showing the long-term value of perioperative inotropic therapy, such therapy must be used with caution, especially in clinical situations of myocardial ischemia–reperfusion injury.⁴

The authors used the Western Denmark Heart Registry, a prospective, compulsory national registry with robust clinical data element definitions, routine data validation, and exceptional data-completion rates. There are national data accuracy audits, sampling assessments, and missing data analyses. The data elements collected were clinically relevant, including duration of inotropic therapy, dosing, and agent specificity. This strong data foundation was combined with contemporary analytical techniques to address the confounding treatment bias, and systematic bias expected in observational analyses of treatment. They were able to address differences in patient risk or procedural complexity and demonstrate well-balanced matched cohorts using standardized difference measurements. Finally, they evaluated three specific subgroups of inotropic therapy: intraoperative only, intraoperative combined with postoperative, and postoperative only.

Despite these strengths, significant limitations preclude these data from sounding the death knell for inotropic therapy during and after cardiac surgery. First, residual confounding despite adequate matching may overestimate the effect size observed by the authors. Although acceptable standardized differences in the propensity-matched cohorts were observed, the clinical definitions of the registry variables often do not enable comparison of severity within a given disease category. For example, the authors adequately balanced the proportion of patients with “chronic obstructive pulmonary disease” as defined by the EuroSCORE. However, their data and analysis do not allow any conclusions regarding the severity of pulmonary disease within the group of patients that received inotropes *versus* those that did not. The same is true for other patient risk factors that may have a wide range of severity: extracardiac arteriopathy, neurologic dysfunction, critical preoperative state, and unstable angina. As a result, it is likely that some degree of residual confounding and treatment bias remained in the analysis due to provider clinical biases for use of inotropes in patients with increased disease burden. This would result in an overestimation of harm associated with the inotropes.

Next, the authors’ analyses demonstrate that the harm associated with inotropic therapy was dependent on the administration period: patients with isolated intraoperative therapy had significantly lower risk of mortality than patients with postoperative therapy. Despite this observation, the authors did not

perform a sensitivity analysis that focused on matching patients with isolated intraoperative inotropes with patients without any inotropes. A more nuanced analysis may demonstrate that focused intraoperative therapy is not associated with any harm. Finally, the aggregation of all common inotropes into one large analytical group may mask the differential value or harm associated with each.⁵ Most importantly, vocal calls for changes in inotropic therapy should consider the feasibility of prospective randomized effectiveness trials. The aprotinin saga revealed that adequately powered prospective interventional trials to address controversies in cardiac surgery are feasible. The data presented by Nielsen *et al.* add to the body of literature demanding a well-conducted trial of inotropic therapy in cardiac surgery.

Routine administration of inotropic therapy during cardiac surgery may eventually fall into the growing body of interventions no longer supported by large-scale effectiveness analyses. Given the relatively low incidence of myocardial dysfunction as a cause of acute hemodynamic instability in cardiac surgery, the provocative and well-conducted article by Nielsen *et al.* should certainly cause clinicians to pause and consider the risk and benefit of perioperative inotropes on a case-by-case basis. Novel positive inotropes that balance improved short-term hemodynamics and long-term safety are under clinical investigation and may offer new therapeutic options.⁶ Until then, our efforts to help patients by improving short-term hemodynamics may prove more harmful than we realized. Once again, we may find that for many patients, “less is more.”

Competing Interests

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