

Big data- a cheerleader for translational perioperative medicine.

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Editorial

The study of perioperative medicine outcomes using large databases- so-called “big data”- has emerged as a valuable approach that increasingly challenges long-held clinical beliefs and forces us to rethink mechanistic paradigms underlying postoperative morbidity. In this issue of A&A, the Department of Outcomes Research at the Cleveland Clinic continues to build on their major contribution to the perioperative medicine “big data” portfolio by reporting the results of the largest study yet that focuses on the relationship between rheumatoid arthritis and perioperative outcomes.¹ The authors tested the primary hypothesis that rheumatoid arthritis is independently associated with increased postoperative cardiovascular complications. This hypothesis is highly plausible given the well-established literature in rheumatoid arthritis demonstrating an increased risk of atherosclerosis, coronary artery disease and all-cause cardiovascular morbidity in the non-operative setting.² Patients with rheumatoid arthritis have an elevated risk of myocardial infarction that is equivalent to patients who have diabetes mellitus or those patients without rheumatoid arthritis who are 10 years older.³ The underlying mechanisms are incompletely understood, particularly as the elevated risk of cardiovascular disease in patients with rheumatoid arthritis precedes their diagnosis based on American College of Rheumatology criteria.⁴ This excess risk cannot be explained by conventional risk factors.⁵ Mirroring the myocardial injury phenotype of perioperative patients more generally,⁶ patients with rheumatoid arthritis rarely present with angina and have higher rates of unrecognized cardiovascular disease.⁴

In the Cleveland Clinic’s Department of Outcomes Research analysis, inpatient hospital data across seven US states for 1 year were assessed; each patient with rheumatoid arthritis was propensity matched with a suitable control. Multivariable logistic regression was used to compare matched rheumatoid arthritis and control patients on risk of in-hospital cardiovascular

complications. Approximately 1.2% patients undergoing noncardiac surgery had a coded diagnosis of rheumatoid arthritis; of these, 1095 rheumatoid patients were propensity matched with 1006 control patients. Unexpectedly, patients with rheumatoid arthritis were not found to be at more risk of cardiovascular complications (odds ratio: 1.08 [95% CI: 0.96-1.21]; P=0.08), with a similar incidence of thromboembolic complications and mortality. These findings mirror those from the Veterans Affairs Surgical Quality Improvement Program, where patients with rheumatoid arthritis were more likely to require a return to the operating room yet had similar rates of VASQIP-defined postoperative infection, cardiovascular events, and mortality.⁷ These findings were broadly similar to those of a systematic review and meta-analysis of forty studies comparing complications following total joint arthroplasty for rheumatoid arthritis versus for osteoarthritis.⁸ Although this systematic review is rather hampered by a lack of studies explicitly defining rheumatoid arthritis, and/or adjusting for covariates, patients with rheumatoid arthritis appeared to be at higher risk of infection following total knee arthroplasty. This observation was strengthened by an earlier need for revision of total knee arthroplasties in patients with rheumatoid arthritis. Avoiding revision procedures in patients with rheumatoid arthritis may be particularly important as they appear to be at increased risk of prosthetic joint infection.^{9,10}

Taken together these findings would appear to suggest that perioperative physicians may have unduly judged patients with rheumatoid arthritis to be at higher risk of postoperative cardiovascular morbidity, and other morbidities linked to perioperative cardiovascular complications including infections.¹¹ However, closer inspection of the VASQIP database, which followed patients post-procedure for 3.7 ± 2.7 y, reveals that rheumatoid arthritis was associated with a significantly higher long-term mortality (hazard ratio: 1.22 (95% CI: 1.00-1.49)). These data again reinforce the importance of considering the consequences of noncardiac surgery

beyond the time period over which administrative databases typically capture hospital morbidity.^{12,13} In addition, we cannot be sure that surgical and/or anaesthesiology bias in preoperative patient screening apparently minimizes adverse perioperative outcomes by selecting out the patients with rheumatoid arthritis who have the most severe disease characterized by chronic multi-organ dysfunction. Only the presence, rather than severity, of rheumatoid arthritis was captured by the Cleveland Clinic study. In particular, multisystem organ dysfunction commonly found in rheumatoid disease including chronic kidney disease¹⁴ are clearly associated with worse perioperative outcomes even in patients without rheumatoid arthritis.¹⁵ Furthermore, the Cleveland Clinic study did not report on the risk of perioperative infectious complications. A retrospective longitudinal cohort study found substantially risk for objectively confirmed infections (adjusted hazard ratio:1.70 (95%CI:1.42-2.03)) and infections requiring hospitalization in patients with rheumatoid arthritis (adjusted hazard ratio:1.83 (95% CI 1.52-2.21)). Musculoskeletal, skin and respiratory infectious complications were most prevalent.¹⁶

The relative lack of data on the impact of medication for rheumatoid arthritis and perioperative outcomes is notable. The American College of Rheumatology guidelines recommend that rheumatoid arthritis patients stop taking biologic therapies one week before surgery, and not restart them until a week after surgery.¹⁷ However, the role of other disease modifying drugs (DMDs) remains unclear with generally retrospective or unblinded, low quality studies providing limited information.¹⁸ The systemic anti-inflammatory effect of DMDs may reduce cardiovascular morbidity over the longer term.¹⁹ Two studies have associated preoperative cessation of biologic therapies with postoperative flare-ups of psoriasis²⁰ and rheumatoid arthritis.²¹ Counter-intuitively, continuing methotrexate may reduce the risk of postoperative infection and reduce flare-ups within six weeks of surgery.²¹ Several of these drugs are now

being considered for repurposing,²² which may be of underappreciated benefit in noncardiac surgery. Translational experimental models also show that the immunosuppressive properties of chloroquine may decrease susceptibility to sepsis following hemorrhage.²³

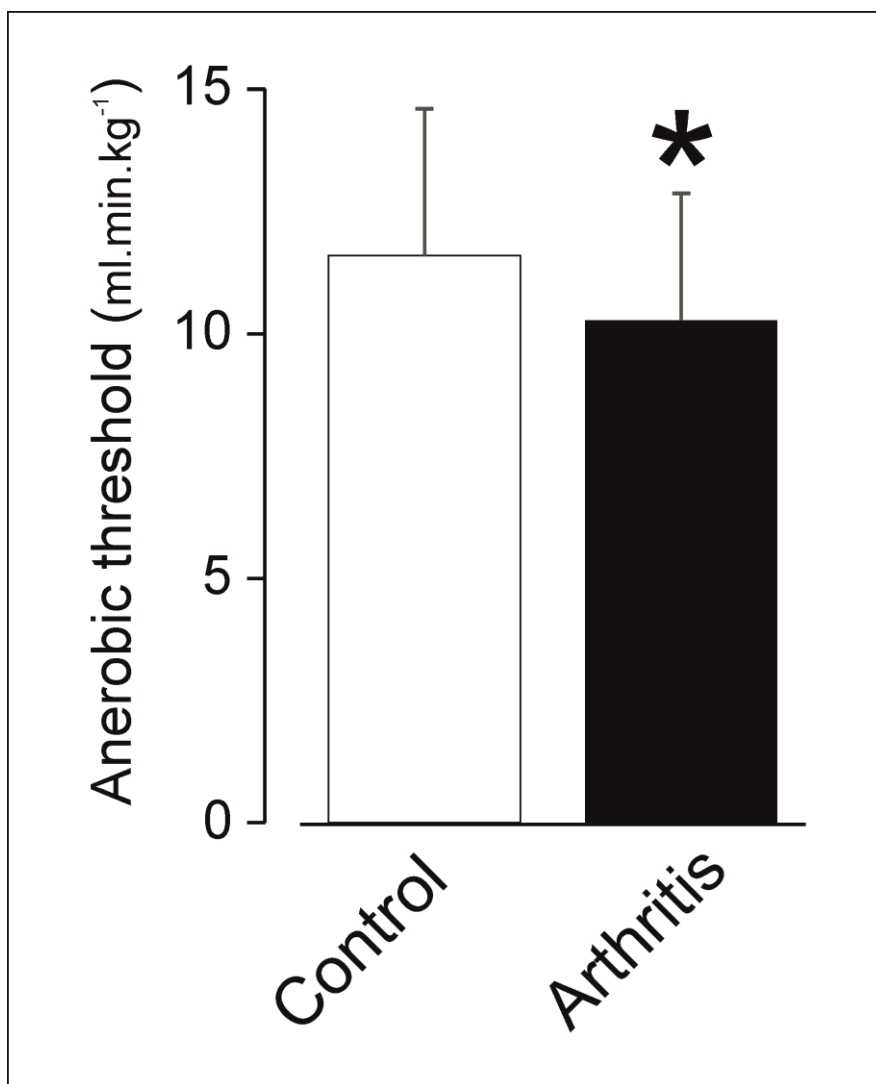
The suggestion that longer-term, post-discharge outcomes are worse in patients with rheumatoid arthritis is of particular importance and concern, suggesting that the database approach can easily miss critical time windows. Furthermore, clinical comparisons need to be underpinned by a clear biologic rationale. Although rheumatoid arthritis is often compared with osteoarthritis, the biologic basis for this may be flawed. Laboratory models have established that osteoarthritis is a chronic inflammatory disease, sharing immunologic overlap with other diseases of autoimmunity.²⁴ Most strikingly, further subgroup analysis in the Cleveland Clinic study suggests that patients with rheumatoid arthritis and co-existing cardiovascular disease sustain more postoperative cardiovascular complications than control patients who do not have rheumatoid arthritis and co-existing cardiovascular disease. Our preoperative assessment of higher-risk surgical patients by cardiopulmonary exercise testing shows that cardiopulmonary reserve is lower in 199/759 patients with arthritis (Figure 1). Controlling for age-related decline in cardiopulmonary reserve, plus established cardiovascular pathology and diabetes mellitus, anaerobic threshold is $1.3 \text{ ml} \cdot \text{kg} \cdot \text{min}^{-1}$ lower (95%CI:0.8-1.75); $p=0.015$) in patients with arthritis (most frequently osteoarthritis). Given the association between low aerobic capacity ($\leq 11 \text{ ml} \cdot \text{kg} \cdot \text{min}^{-1}$) and postoperative complications,²⁵ it is striking that patients with arthritis are more likely (relative risk: 1.68 95%CI: 1.28-2.20); $p<0.0001$) to demonstrate poorer cardiopulmonary reserve. These data suggest that the chronic pro-inflammatory process common to all arthritides may lead to a deconditioning phenotype and hence poorer cardiovascular performance under stress. Deconditioning may result from lower physical activity or accelerated cardiovascular disease leading to subclinical chronic cardiac failure.

These studies highlight potential strengths and significant limitations of the large database approach. The apparent disconnect between the rheumatoid arthritis “big data” literature and established perioperative risk factors highlights two key contributions perioperative medicine can make in a broader context. First, there is a clear need for a better understanding of how the progression of complex, multi-system diseases is altered by the perioperative phase and its’ management. Second, the unique translational potential of the perioperative arena not only offers an unrivalled opportunity to understand pathologic mechanisms and reduce postoperative complications, but also provide other specialties invaluable biologic insights as to whether apparently paradoxical “big data” findings should shape their clinical practice. Mechanistic interrogation catalyzed by unexpected findings from observational and trial datasets have transformed many other areas of medicine, statin therapy for hypercholesteremia perhaps being the most notable.²⁶ Perioperative medicine requires a similar non-siloed, complementary approach as bioinformatic analyses of large electronic databases generate plausible- though not necessarily conventional and/or predictable- hypotheses. Bed-to-benchside translational investigators should be an integral part of this process, through which ‘big data’ can reinvigorate the role of experimental perioperative medicine. We therefore suggest that perioperative “big data” studies would greatly benefit from the contribution of experimental perioperative medicine investigators in cross-cutting, multi-disciplinary study designs from inception.

Figures and Illustrations

Figure 1. Association between arthritis and anaerobic capacity.

Unadjusted values shown for 199/759 patients with arthritis (osteoarthritis or rheumatoid) who underwent cardiopulmonary exercise testing at University College London Hospitals NHS Trust preoperative assessment for noncardiac surgery. Mean \pm SD values shown.



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