

## Endocarditis is not an Independent Predictor of Blood Transfusion in Aortic Valve Replacement Patients With Severe Aortic Regurgitation

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**Objective:** This study sought to evaluate if the presence of endocarditis was independently associated with increased perioperative blood transfusion in patients undergoing aortic valve replacements (AVR) with aortic regurgitation.

**Design:** This was a retrospective study.

**Setting:** Large Canadian tertiary care hospital.

**Participants:** Six hundred sixty-two consecutive patients with aortic regurgitation score of 3 or higher undergoing AVR from 1995 to 2012.

**Interventions:** No interventions were performed in this retrospective study.

**Measurements and Main Results:** After REB approval, data were obtained from a center-specific database. Univariate analysis was performed to identify variables that may be associated with transfusion of any allogeneic blood product perioperatively. A multivariate logistic regression was generated to identify independent predictors of perioperative transfusion. Unadjusted transfusion rates in patients with no endocarditis and with endocarditis were 32% and 70% ( $p < 0.001$ ), respectively.

Independent predictors of any transfusion were moderate-to-severe preoperative anemia, preoperative renal failure, non-isolated AVR, age  $> 70$ , urgent/emergent surgery, BMI  $< 25$ , and female sex. Endocarditis was not an independent predictor of transfusion (OR = 0.748; 95% CI = 0.35-1.601).

**Conclusions:** In patients undergoing AVR, unadjusted perioperative transfusion rates were higher when endocarditis was present. However, after adjustment, aortic valve endocarditis was not independently associated with blood transfusion. The authors' observation could be explained by the higher prevalence of many independent predictors of transfusion, such as comorbidities or more complex surgery, within the endocarditis group. Thus, AV endocarditis, in the absence of other risk factors, was not associated with increased perioperative transfusion risk.

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**KEY WORDS:** endocarditis, transfusion, aortic valve replacement, aortic regurgitation, aortic insufficiency

**P**REOPERATIVE IDENTIFICATION of patients at a high risk of receiving perioperative blood transfusions during cardiac surgery is a Level A recommendation from the Society of Thoracic Surgeons Blood Conservation Guideline Task Force.<sup>1</sup> There are several notable indicators of blood transfusion requirements in cardiac surgery, such as advanced age, preoperative anemia, small body size, complex procedure, preoperative antiplatelet therapy, acquired or congenital coagulation/clotting abnormalities, and multiple comorbidities.<sup>1</sup> Several studies have identified endocarditis as an additional risk factor for bleeding.<sup>2-6</sup> However, it could be argued that patients with endocarditis typically carry many factors that already are associated with an increased risk of blood transfusion.

Despite improved guidelines and antibiotics, the incidence of endocarditis has remained constant for 30 years at a rate of 2 to 6 individuals per 100,000.<sup>7</sup> The most common pathogens (Streptococcus species, Staphylococcus species, and Enterococcus species) also have remained unchanged over time.<sup>7</sup> Its clinical presentation varies from mild or sub-clinical to emergent and may include clinical features defined in the modified Duke criteria such as fever, vascular phenomena, or immunologic phenomena.<sup>7,8</sup> The risk of coagulation abnormality in patients suffering from endocarditis may be related to the degree of inflammation and may range from a hypercoagulable state in which patients are susceptible to thromboembolic events, to the full picture of septic shock and organ failure with disseminated intravascular coagulation.<sup>9-11</sup> In addition, patients' volume status and, therefore, their tolerance to additional fluid, may vary considerably from fluid overloaded due to congestive heart failure to volume depleted due to septic shock. It is important to support and treat both situations to prevent secondary organ failure. Complicating the situation further is the fact that the extent of surgery required varies according to the level of anatomic destruction. It can range from simple removal of the

vegetation, valve replacement, extended patch repair or aortic replacement, up to multiple valve interventions,<sup>12</sup> possibly requiring prolonged periods of cardiopulmonary bypass and aortic cross-clamping. Endocarditis patients often show characteristics such as preoperative anemia, increased age, multiple comorbidities and organ dysfunction.<sup>7,13</sup> Taken together, the presence of valvular endocarditis may impact transfusion requirements perioperatively in a variety of ways.

Perioperative blood conservation measures, such as preoperative autologous blood donation, ultrafiltration, cell saver use, and various antifibrinolytics, have been shown to effectively reduce blood transfusion utilization.<sup>1,14,15</sup> However, these conservation measures should be allocated appropriately, and it is important to limit their use in low-risk patients.<sup>15</sup> Additionally, it is particularly important to limit blood transfusions in patients with underlying endocarditis since this could further aggravate their already compromised organ function.<sup>8</sup>

This retrospective study sought to evaluate if the presence of endocarditis was associated with increased perioperative blood transfusion in aortic valve replacements (AVR) and would, therefore, warrant enhanced blood conservation strategies. The authors hypothesized that there would be a positive association between endocarditis and blood transfusion based on past evidence.

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1053-0770/2601-0001\$36.00/0

<http://dx.doi.org/10.1053/j.jvca.2015.10.003>

## METHODS

This study was undertaken following ethical approval and waiver of the requirement for written informed consent from patients by the Capital Health Research Ethics Board in June 2013. This was a retrospective study of 662 consecutive patients undergoing isolated aortic valve replacement (AVR), AVR plus pericardial patch, or AVR plus aortic root repair or replacement. Aortic valve lesions were the most common lesion requiring surgery, and other valvular lesions were excluded to produce a more homogeneous sample. The Maritime Heart Center Cardiac Surgery Registry database is a prospectively collected database established in 1995 at a large Canadian center. Detailed blood transfusion data were collected by chart review.

All included patients had aortic insufficiency (AI) graded as 3 or 4 on a 4-point scale at the time of reported echocardiography in order to ensure comparison between endocarditis and non-endocarditis patients. Exclusion criteria were AVR for aortic dissection, remote endocarditis (last active endocarditis infection more than 6 months prior to surgery), or aortic stenosis as the primary pathology.

Patients were documented as having endocarditis based on a combination of clinical criteria, echocardiography data, and bacteriology data. The following preoperative variables were collected from the Maritime Heart Center Cardiac Surgery Registry database: age (years), weight (kg), height (cm), gender, redo sternotomy, type of surgery (isolated AVR, AVR + pericardial patch, and AVR + aortic root repair/replacement), procedure urgency (elective *v* urgent/emergent), surgery date, serum creatinine ( $\mu\text{mol/L}$ ), left ventricular ejection fraction (%), hemoglobin (g/L), chronic obstructive pulmonary disease, congestive heart failure, hypertension, diabetes mellitus, and peripheral vascular disease. These variables were selected due to their potential association with increased transfusion as identified in prior literature.<sup>1</sup> Patients were graded as non-anemic (Hb >20 g/L for women, Hb >130 g/L for men), mildly anemic (Hb 110-119 g/L for females, Hb 110-129 g/L for males) or moderately-severely anemic (Hb <109 g/L). Patients were identified as having preoperative renal failure if their serum creatinine was above 176  $\mu\text{mol/L}$ .

### Anesthetic Techniques, Blood Conservation Strategies, and Transfusion Triggers

Balanced general anesthesia was employed in all cases using fentanyl/sufentanil, propofol, pancuronium/vecuronium/rocuronium, midazolam, and volatile inhalation agents (isoflurane, sevoflurane, desflurane). A hemoglobin level below 70 g/L was used as a transfusion trigger for packed red blood cells since early 1999; prior to that, patients received transfusion with a hemoglobin level below 90 g/L. Blood products to enhance coagulation activity, such as fresh frozen plasma, platelets and cryoprecipitate, were administered according to the degree of coagulopathy and based on clinical decision-making by attending anesthesiologists and surgeons. Salvage of red blood cells from shed mediastinal blood, administration of return pump blood after completion of CPB, and antifibrinolytics were used in all patients. In 2007, a switch was made

from epsilon-aminocaproic acid (100 to 150 mg/kg bolus followed by a continuous infusion of 10 mg/kg per hour) to tranexamic acid (bolus of 10 mg/kg, mostly followed by an infusion of 1 mg/kg per hour). Aprotinin was used only in approximately 1% of cases. For blood conservation, preoperative autologous blood donation was used infrequently in selected cases. A cell saver was used whenever major bleeding occurred after completion of cardiopulmonary bypass.

### Statistical Analysis

All candidate prognostic variables were categorical and were examined for association with any blood transfusion using univariate analysis by Fisher's exact test or  $\chi^2$  as appropriate. In-hospital mortality also was examined univariately. All patients then were grouped into patients treated for endocarditis (endocarditis group) and those without endocarditis (non-endocarditis group). Propensity score matching, as well as manual matching, of the endocarditis and nonendocarditis groups was unsuccessful due to excessive intergroup variation on a number of independent preoperative variables. The primary outcome was any allogeneic blood transfusion (red blood cells [RBCs], cryoprecipitate, plasma, and platelets) intraoperatively or throughout the entire postoperative hospital stay. A non-parsimonious multivariate logistic regression model was created to examine the association of endocarditis with blood transfusion after adjusting for the previously identified preoperative variables. Model discrimination was assessed by the area under the receiver operating characteristic (ROC) curve. A bootstrap procedure was performed to obtain 1,000 subsamples with replacement, and the 95% confidence interval (CI) of the ROC was obtained from the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the bootstrap distribution.

The median quantity of blood products received was calculated for patients undergoing isolated AVRs and compared to those undergoing AVRs  $\pm$  patch  $\pm$  root using the Wilcoxon rank sum test. Statistical analysis was undertaken using the software SAS, version 9.3 (SAS Institute Inc., Cary, NC).

## RESULTS

During the study period, a total of 3,915 patients underwent aortic valve surgery, with 662 meeting the inclusion criteria. Preoperative clinical characteristics for the 662 patients included in the study are presented in Table 1. From this group, the authors identified 92 patients (14% of total sample) with endocarditis. Non-isolated AVR, urgent/emergent procedures, moderate-to-severe anemia, and preoperative renal failure were more prevalent in the endocarditis group than in the nonendocarditis group ( $p < 0.001$  for all). In contrast, patients in the nonendocarditis group were older ( $p = 0.025$ ).

The overall transfusion rate was 37% for the 662 included patients. Unadjusted blood transfusion rates were 32% ( $n = 181/570$ ) and 70% ( $n = 64/92$ ) for patients without endocarditis and with endocarditis, respectively. The median number of units of blood products received by the endocarditis group was dependent on the complexity of surgery (isolated AVR *v* AVR  $\pm$  patch  $\pm$  root) (Table 2). Overall, endocarditis patients undergoing non-isolated AVR received more units of blood

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