

Impact of Aortic Valve Replacement on Glycemic Control in Diabetes Mellitus

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ABSTRACT

Introduction: The Framingham Studies revealed that diabetes mellitus (DM) predisposed subjects to a two- to eight-fold increase in the risk of developing heart failure (HF). However, there is much less information available about the reverse issue; namely, whether there is an increased risk of developing DM in patients with HF. We sought to determine if reversal or partial reversal of HF through aortic valve replacement (AVR) would improve glycemic control in patients with DM at our institution.

Methods: The electronic medical records of 57 consecutive diabetic patients were retrospectively analyzed. These patients had undergone AVR at a medium-sized academic medical center from May 2005 through May 2015, and had glycated hemoglobin (HbA1C) measured before and after the procedure. The variables of interest included HbA1C, and echocardiographic parameters such as left ventricular ejection fraction (LVEF), tricuspid regurgitation velocity (TRV), and right ventricular systolic pressure (RVSP) before and after valve replacement.

Results: HbA1C decreased significantly during the first year after replacement, from 7.1% (range 4.4 - 13.0%) before surgery to 6.5% in the first year ($P < .05$). In addition, the calculated RVSP decreased from 44 mmHg (20 - 79 mmHg) to 37 mmHg ($P < .05$ from the preoperative value). LVEF and TRV did not change significantly. Reductions in HbA1C and RVSP during the first year were greater in patients who experienced an increase of 5% or more in EF at their first postoperative measurement. Patients with higher baseline HbA1C values had a greater decline in glycated Hb during the first year ($P < .01$).

Conclusion: AVR was associated with a reduction of HbA1C and a decrease in pulmonary artery systolic pressure within one year of the procedure.

INTRODUCTION

The Framingham studies initially revealed that diabetes mellitus (DM) predisposed individuals to heart failure (HF), increasing the risk by two- to eight-fold. A 1% increase in

glycated hemoglobin (HbA1C) was linked to an 8% increase in risk for congestive HF. However, much less information is available about the reverse issue; namely, an increased risk of developing DM in patients with HF.

A recent cohort of 58,056 non-diabetic patients showed an increased incidence of DM in patients with established HF [Nichols 2011]. Moreover, it has been shown that the correction of HF with left ventricular assist devices appears to improve glycemic control in diabetic patients [Uriel 2011]. These two facts eventually led to the proposal of the term “cardiogenic diabetes” in 2014 [Guglin 2014].

Aortic valve disease can be caused by aortic stenosis (AS), aortic regurgitation, or both [Nishimura 2014]. Valvular stenosis results in chronic left ventricular hypertrophy and congestive symptoms [Stewart 1997]. Chronic aortic regurgitation results in volume overloading of the left ventricle, left ventricular dilation, and eventual HF [Dujardin 1999; Tornos 1995; Bonow 1991; Siemenczuk 1989]. Both conditions can be corrected surgically or via invasive procedure, and hence represent a potentially reversible cause of HF. The conditions are therefore amenable to study.

The objective of this study is to follow HbA1C in diabetic patients undergoing aortic valve replacement (AVR) at our institution to see if there was an improvement in glycemic control, in an effort to elucidate more fully the link between HF and DM.

MATERIALS AND METHODS

Prior to the initiation of this study, Institutional Review Board approval was obtained to complete a retrospective medical record review of AVR cases from May 2005 through May 2015. The University Center for Clinical and Translational Science Enterprise Data trust was subsequently utilized to identify a consecutive series of distinct diabetic patients who underwent valve replacement during the 10-year period. Upon identification of individual cases, a trained medical reviewer then reviewed the corresponding HbA1C measurements. Subjects that did not have both pre and postoperative glycated hemoglobin laboratory values dating within one year of the procedure were removed. HbA1C measurements taken within two weeks after the procedure were also excluded, in order to compensate for the possibility that blood products that were received intra- and peri-operatively might alter HbA1C values.

Variables of interest included HbA1C, Ejection Fraction (EF), Tricuspid Regurgitation Velocity (TRV), and Right

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Ventricular Systolic Pressure (RVSP) before and after valve replacement. The two latter variables were included as a surrogate for congestion, because they reflect pulmonary arterial systolic pressure. The RVSP was calculated based on the formula $4v^2 + \text{central venous pressure}$, where v is the maximal velocity of tricuspid regurgitation, and central venous pressure is estimated based on the inferior cava diameter. We analyzed the data for the first and second postoperative year.

Statistical Analysis

The data were collected using Excel Software (2010 Microsoft Corporation). All data were analyzed using the Statistical Program of Social Sciences version 21 (SPSS™, IBM Inc., Armonk, NY, USA). Paired t-tests were used to compare patients' preoperative measures to the average of the first and second year measurements. The number of first year paired measurements ranged from 24 to 53, and second year pairs ranged from 18 to 27. Sub-analysis compared paired changes between patients that gained more than 5% in EF at their first postoperative measurement to those that gained less than or equal to 5% in EF. In a separate analysis, baseline (before the surgery) HbA1C was dichotomized into above the median and below the median values, and changes in postoperative HbA1C were analyzed for the upper and lower baseline HbA1C cohorts separately. For all analyses, $P < .05$ was considered statistically significant.

RESULTS

Between May 2005 and May 2015, 795 patients with an established diagnosis of DM underwent AVR at our institution. Only 57 of these patients had HbA1C recorded both before and after AVR. Of the 57 subjects with both preoperative and postoperative HbA1C values, 14 patients received transcatheter aortic valve replacement (TAVR), and 43 underwent traditional open heart surgery.

In our final cohort of 57 patients, the mean age was 63.5 ± 13.2 , the mean body mass index was 29.7 ± 6.4 kg/m², 37 (64.9%) were male, and 40 (70.1%) were smokers.

Before surgery, the mean HbA1C was 7.1% (range 4.4 - 13.0%). During the first year after surgery, it decreased to 6.5% ($P < .05$), and during the second year, it was 6.9% ($P = \text{NS}$).

The mean LVEF before AVR was 49% (range 10 - 70%), increasing to 51% in the first year after the surgery and 54% in the second year, with neither reaching significance. The mean TRV was 274 cm/sec initially, 248 cm/sec in the first postoperative year, and 260 cm/sec in the second postoperative year, and the mean calculated RVSP decreased from 44 mmHg (20-79 mmHg) to 37 mmHg ($P < .05$ from the preoperative value) and 40 mmHg, respectively.

Although the magnitude of change in HbA1C was similar in the first and second year after the surgery, statistical significance was achieved only for the first year, likely because sample size decreased from the first to the second year (Table 1).

Reductions in A1C, TRV, and RVSP values during the first year all tended to be greater in patients who experienced an increase of 5% or more in EF at their first postoperative measurement

Table 1. Dynamics of HbA1C and Echocardiographic Parameters from Preoperative to Postoperative Values

Measure	Preop Mean (range)	Paired Change in Year 1 Values versus Preop. (95% CI)	Paired Change in Year 2 Values versus Preop. (95% CI)
EF	49 (10 - 70)	0.3 (-3.1 - 3.7)	0.8 (-4.4 - 6.1)
A1C	7.1 (4.4 - 13)	-0.4* (-0.8 - -0.1)	-0.4† (-0.9 - 0.0)
TRV	274 (155 - 400)	-22 (-49 - 5)	-2 (-34 - 30)
RVSP	44 (20 - 79)	-6.9* (-13 - -1.3)	-5.8† (-12 - 0.8)

*Paired t-test difference $p < 0.05$; † Paired t-test difference $p < 0.10$

during the first year. None of these differences were significant, again, likely due to the reduced sample size (Table 2).

The median HbA1C for all 57 patients was 6.6 (range 4.4 - 13.0). The stratification of patients into the upper (HbA1C > 6.6) and the lower half (HbA1C < 6.6) of the sample group yielded 24 and 33 patients, respectively. Patients in the upper half of the sample group had mean year one changes equal to -1.1 (SEM 0.3). Patients in the lower half had mean year one changes equal to -.0 (SEM 0.2). The paired t-test differences in mean change were significant, with $P = .001$. In other words, patients with higher initial HbA1C experienced a much greater decrease after AVR.

DISCUSSION

In this retrospective study, we found that HbA1C declined (glycemic control improved) in diabetic patients within the first year after AVR, regardless of the technique (surgical versus percutaneous). At the same time, favorable hemodynamic changes occurred. Namely, pulmonary arterial systolic pressure, which was used as a surrogate of congestion, decreased. Those patients whose LVEF increased after the surgery tended to have a greater reduction in HbA1C. Diabetics with higher preoperative HbA1C values had greater reductions than those with normal or near-normal preoperative values.

Diabetes mellitus is a well-known risk factor for the development of HF [Bertoni 2004; Nichols 2001; Kannel 1979]. Conversely, several previous studies have led to the hypothesis that congestive heart failure itself can cause insulin resistance, and may be an independent risk factor for the development of DM [Guglin 2014; Andersson 2010; AlZadjali 2009; Amato 1997]. In support of this hypothesis, LVAD implantation has demonstrated that the normalization of cardiac output in patients with advanced HF leads to improved diabetic control [Choudhary 2014; Mohamedali 2014; Uriel 2011].

Conceptually in line with these experiments, in this study we examined the effect of AVR on diabetes control by

Table 2. Changes in A1C, TRV, and RVSP Over 1st Year Compared to Preoperative Value Stratified by First Measured Change in EF

Mean Paired Changes in Year 1 Measurements versus Preop. (SEM)	In Patients with \geq 5% gain in EF at first measurement	In Patients with $<$ 5% gain in EF at first measurement	t-test P-value
A1C	-8 (.3) 13 pairs	-.2 (.3) 25 pairs	.124
TRV	-27 (29) 9 pairs	-19 (13) 15 pairs	.782
RVSP	-6.8 (5.5) 10 pairs	-6.5 (3.4) 15 pairs	.962

A1C indicates glycated hemoglobin; TRV, tricuspid regurgitation velocity; RVSP, right ventricular systolic pressure.

retrospectively measuring changes in HbA1C in 57 patients at our institution. In this study, AVR resulted in significantly lower HbA1C measurements for patients within one year of the procedure. These data therefore lend support to the hypothesis that the restoration of cardiac function may lead to improved diabetic control in patients with HF.

The mechanisms responsible for the reversal of glycemic control remain unclear, although it is likely both complex and multifactorial. It is probable that enhanced blood flow to the pancreas and other organs improves the production and transportation of endogenous hormones to the body [Heck 2009]. It is also possible that improvements in cardiac output decrease circulating levels of neurohormones and inflammatory markers such as noradrenalin, angiotensin, and tumor necrosis factor alpha [Torre-Amione 1999; James 1995]. It has previously been shown that neurohormonal suppression with ACE-Is or ARBs reduces the risk of developing DM by more than 25% in HF patients, and one study by Koerner et al demonstrated a reduction in serum cortisol and catecholamine levels after LVAD implantation [Koerner 2014; Andraws 2007].

Another potential mechanism, and a likely confounder in our study, is the role of physical activity after AVR. With a decline in patient morbidity, physical activity has been shown to increase after valve replacement [Long 2014]. This result may favorably impact insulin resistance, but does not directly support the hypothesis of HF as an independent risk factor for the development DM. Prospective studies that measure physical activity and body composition to assess changes in fat versus muscle mass after AVR would be needed to mechanistically address the individual contributions of these factors to the observed changes in glycemic control.

Like other retrospective studies, ours was subject to inherent limitations. The sample size was small due to lack of consistent baseline and follow-up HbA1C measures. Patient information was collected utilizing electronic chart review, and this carries the potential for suboptimal data collection due to incomplete or missing medical records. Additionally, while our retrospective data may clearly provide proof of concept for decreased DM and possibly its reversal in HF, it does not provide insights into other candidate mechanisms that are likely contributing to our observations. Despite these limitations, we believe that this study suggests important links between surgically

correctable causes of HF and improvement in glycemic control in patients with DM.

CONCLUSION

Favorable hemodynamic changes after AVR are associated with improvement in diabetic control within one year of procedure. The exact mechanism by which replacement leads to improvement in diabetic control is not known, and it is probable that a number of factors play a role, such as improved pancreatic blood flow and decreased endogenous neurohormones/inflammatory markers. Further prospective studies to validate our findings and determine the etiology for improved diabetic control will likely improve our understanding of DM in relation to HF.

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