Association of Mitral Valve Prolapse With Infective Endocarditis Due to Viridans Group Streptococci

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Although patients with certain cardiac valve abnormalities have increased risk of infective endocarditis (IE), it is unknown whether these abnormalities are associated with specific pathogens in IE cases. We report a strong association between mitral valve prolapse and viridans group streptococcal IE in a population-based cohort from Olmsted County, Minnesota.

Keywords. endocarditis; valvulopathy; viridans group streptococci.

Mitral valve prolapse (MVP) affects approximately 2%–3% of the US population and can be familial or sporadic. It is diagnosed using 2-dimensional echocardiography with either single or bileaflet prolapse of at least 2 mm beyond the long-axis annular plane [1]. In a case-control study of infective endocarditis (IE) and cardiac risk factors, patients with IE were significantly more likely to have MVP, rheumatic carditis, history of congenital heart disease, a prior episode of IE, cardiac valvular surgery, or other valvular heart disease [2]. Findings from a descriptive analysis of the literature performed more than 2 decades ago suggest that there may be an association between MVP and IE due to viridans group streptococci (VGS) [3]. We analyzed data obtained from the Olmsted County, Minnesota, population, a population that we have examined in the past to define unique epidemiologic features in serial population-based surveys that have included patients from 1970 to the present [4, 5].

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METHODS

All Olmsted County residents aged ≥18 years with definite or possible IE, as defined by the modified Duke criteria [6], between 1 January 1970 and 31 December 2013 were identified using the Rochester Epidemiology Project and the Endocarditis Registry of the Division of Infectious Diseases at Mayo Clinic, which has been described previously [4, 5]. The entire medical record was available for review.

It should be emphasized that between 1970 and 2013, the diagnostic criteria of MVP evolved as different modalities in cardiac imaging became available—M-mode and 2-dimensional. Therefore, each patient's echocardiogram in our population-based survey was reviewed by team members (C. V. D. and N. S. A.) to determine if MVP was present based on the definition as described by Bonow et al [7]. These team members were blinded to the microbiologic diagnosis of IE. Cases of MVP occurred in the following years: 1973, 1983, 1986, 1987, 1991, 1992, 1993, 1995, 1996, 1997, 2001, 2003, 2004, and 2006. In 1973, M-mode was used in 1 case; thereafter, 2-D echocardiography (transthoracic and/or transesophageal) was used.

The association of candidate predictor variables with VGS pathogen in IE cases was analyzed with binary logistic regression, with model inputs based on a fixed, a priori selection of valve abnormalities. To ensure reliable estimation of regression coefficients, we limited the number of candidate predictors to be in reasonable balance with the number of observed events (ie, lesser of the 2 frequencies for those with and without VGS). Based on the general guideline of at least 10–15 events per predictor degree of freedom, the availability of 65 events (ie, 65 of 197 IE cases with VGS pathogen) would permit at most about 4–6 predictor terms in the model to avoid overfitting. Five valve abnormalities—MVP, bicuspid aortic valve, congenital heart disease, rheumatic carditis, and previous IE—were selected based on clinical relevance and review of descriptive statistics.

Using logistic regression analysis to assess their influence on likelihood of a VGS pathogen, the 5 valve abnormality terms were entered separately in univariable models and then jointly in a full multivariate model, from which we reported the odds ratios (ORs) and 95% confidence intervals (CIs). To ensure there was no evidence of multicollinearity among the 5 valve

abnormality variables, model diagnostics such as variance inflation factor and condition index were inspected. As a secondary analysis, we augmented the original multivariable model with adjusting variables for age, sex, and year of diagnosis to assess their potential confounding effects. Likewise, we compared the effects of MVP on odds of VGS in multivariable models with and without inclusion of venous insufficiency, as measured by presence or degree of mitral regurgitation (MR). An alpha level of .05 was used to determine statistical significance.

RESULTS

A total of 197 incident cases of IE in Olmsted County from 1970 to 2013 were identified; average age was 63 years and the majority (65%) were male and white (92%). Of the pathogens identified, the causative etiology was VGS in 65 (33%) and non-VGS in 132 (67%) cases. Presence of MVP was seen in 18% of VGS-IE cases and 5% of non–VGS-IE cases, corresponding to an OR of 4.04 (95% CI, 1.51–10.84; $P = .005$) in univariable analysis. Adjusting for the other 4 factors in a multivariable model, the odds of VGS as causative etiology remained 4-fold higher in IE cases with MVP vs those without (OR, 4.22; 95% CI, 1.54–11.55; $P = .005$). Also from this multivariable model, congenital heart disease (OR = 2.18, .75–6.35, $P = .152$), bicuspid aortic valve (OR 1.56, .52–4.70, $P = .427$), rheumatic carditis (OR 1.13, .37–3.41, $P = .831$), and previous IE (OR 0.69, .20–2.40, $P = .557$) were not significantly associated with VGS-IE (Table 1). In the model augmented with age, sex, and calendar year as adjusting variables, each of the 5 valve abnormality variables showed ORs and 95% CIs that were similar to those in the original model, including the revised effect of MVP, which remained significant (OR = 5.26; 95% CI, 1.73–15.98; $P = .003$).

The presence and degree of MR was also examined to determine if the perceived association between MVP and VGS was due, in part, to the degree of valvular insufficiency, rather than MVP itself. The incidence of MR in the VGS group was 36/65 (55.4%) vs 86/132 (65.2%) in the non-VGS group. In a multivariable model that included presence (any degree) of MR in addition to the 5 valve abnormality variables, the revised effect of MVP was attenuated but had retained significance (OR = 3.56; 95% CI, 1.28–9.95; $P = .015$). In those with MVP, there was no significant difference in MR between the VGS and non-VGS groups using χ^2 testing (χ^2 statistic 2.0781; $P = .15$). Furthermore, there was no difference in the degree of MR among the other 4 cardiac conditions. Although we did not find a difference in the degree of MR, it is likely that our study was underpowered to detect a difference of MR between the 2 MVP groups, and thus, a larger cohort will be needed to further evaluate this postulate.

DISCUSSION

In this population-based study, we observed a strong association of MVP and VGS-IE compared with non–VGS-IE cases. Interestingly, in 1986, Baddour and Bisno [8] reviewed the published literature that included 267 cases of IE complicating MVP; 110 cases had a bacteriologic diagnosis. VGS accounted for 46% of IE cases, followed by 10% due to *Staphylococcus aureus* and 9% caused by coagulase-negative staphylococci [8]. Weinberger et al [9] reviewed 135 patients with proven or suspected IE between 1970 and 1987 and found that the bulk of patients with MVP had VGS isolated from blood cultures. Castonguay et al [10] retrospectively reviewed the surgical pathology of native valve endocarditis from 310 specimens at the Mayo Clinic from 1985 to 2004. Of the patients with positive microbiologic cultures, VGS accounted for the majority of cases (28%) followed by *S. aureus* (18%), with MVP present in 43% of IE cases involving the mitral valve [10].

Over the study period, the taxonomy and microbiology of VGS changed. From 1970 to 1979, VGS were identified with negative bile esculin testing, while species-level identification was not performed. From 1980 through 1991, Facklam's scheme [11] was used to determine VGS that identified *Streptococcus sanuis* I & II, *Streptococcus mitis*, *Streptococcus salivarius*,

Table 1. Comparison of Cardiac Valve Abnormalities Between Viridans Group Streptococci (VGS) and non–VGS-Infective Endocarditis Cases

Variable	Viridans (n = 65)	Non-Viridans (n = 132)	Univariable Results[a] OR (95% CI) [*P* Value]	Multivariable Results[a] OR (95% CI) [*P* Value]
Rheumatic carditis	6 (9%)	10 (8%)	1.24 (.43, 3.58) [.690]	1.13 (.37, 3.41) [.831]
Bicuspid aortic valve	6 (9%)	9 (7%)	1.39 (.47, 4.09) [.550]	1.56 (.52, 4.70) [.427]
Mitral valve prolapse	12 (18%)	7 (5%)	4.04 (1.51, 10.84) [.005]	4.22 (1.54, 11.55) [.005]
Congenital heart disease	8 (12%)	8 (6%)	2.18 (.78, 6.09) [.139]	2.18 (.75, 6.35) [.152]
Previous infective endocarditis	4 (6%)	10 (8%)	0.80 (.24, 2.65) [.715]	0.69 (.20, 2.40) [.557]

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Each of the 5 a priori selected variables was analyzed for an association with viridans group streptococci–infective endocarditis status using logistic regression, both individually (unadjusted) in univariable models and jointly in a multivariable model with all 5 valve abnormalities included as predictor variables.

Streptococcus mutans, *Streptococcus uberis*, *Streptococcus acidominimus*, *Streptococcus morbillorum*, *Streptococcus anginosus-constellatus*, and *Streptococcus MG-intermedius*. From 1992 through 1999, classification of VGS included 5 species: *S. mutans*, *Streptococcus milleri*, *Streptococcus sanguis*, *S. salivarius*, *and Streptococcus mitior*. From 2000 through 2011, minor categorization changes of species within the reported species/groups were made by a combination of conventional biochemicals and/or 16S rRNA gene sequencing. From 2012 to the present, species identification with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry was performed. The identity for all 65 VGS cases was confirmed.

The pathogenic mechanisms responsible for this unique association between MVP and VGS as a cause of IE remain undefined. On a molecular basis, there are numerous studies to support the notion that VGS adhesins are important in the pathogenesis of IE [12–15]. Moreover, there is evidence that extracellular matrix proteins are abnormally expressed in MVP and could be important in the predisposition of VGS-IE. However, this remains unproven, and whether other valvulopathies express similar extracellular moieties that can serve as receptors for VGS adhesins has not been examined. Based on the findings of this study, further evaluation of host and organism factors is warranted to better define the pathogenesis of VGS-IE.

Notes

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Author contributions. D. C. D. had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Design and conduct of the study.* D. C. D., I. M. T., D. D. C. d. S., W. R. W., L. M. B. *Acquisition of data.* D. C. D., C. V. D., J. M. S., N. S. A., I. M. T., D. D. C. d. S., L. M. B. *Analysis and interpretation of data.* D. C. D., C. V. D., M. R. S., I. M. T., D. D. C. d. S., B. D. L., W. R. W., L. M. B. *Critical revisions of the manuscript for important intellectual content.* D. C. D., C. V. D., M. R. S., I. M. T., D. D. C. d. S., B. D. L., J. M. S., N. S. A., W. R. W., L. M. B. *Drafting of the manuscript.* D. C. D., C. V. D., W. R. W., L. M. B. *Statistical analysis.* D. C. D., B. D. L., L. M. B. *Obtained funding.* D. C. D., W. R. W., L. M. B. *Administrative technical, or material support.* W. R. W., L. M. B. *Study supervision.* N. S. A., J. M. S., W. R. W., L. M. B.

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