mechanism of leaflet restriction and promotes discussion regarding how to address such elastosis and fibrosis pharmacologically. We also found a high rate of osseous and/or chondrous metaplasia that is noted not to be a feature of aortic BPVs degeneration (5). Overall, pathological features correlated to implant duration, but more valves are required to establish a definitive timeline of each pathological feature. Finally, despite having differing pathological features, pulmonic and tricuspid BPVs showed avidity for ^{18}F-NaF, similar to what we previously demonstrated in aortic BPVs (3). Interestingly, ^{18}F-NaF avidity was observed in leaflets both with and without histological evidence of calcification, supporting our previous finding that ^{18}F-NaF can detect features of SVD independent of calcium deposition appreciable on histology (3).

Overall, we hypothesize the difference in the pathology we find in pulmonic and tricuspid BPVs versus what is known about aortic BPVs in the published reports may be related to flow dynamics, patient demographics, or oxidation state. It is important to note that this study has a number of limitations. First, samples are derived from a tissue registry and thereby represent a sample of convenience and historical cases, and do not necessarily represent the patient population undergoing valve replacement currently. Secondly, explanted valves represent a static moment in time, with ex vivo models and in vivo trials needed in the future to understand the dynamics of the pathology we observe. Future investigations should also consider the role of anticoagulation in SVD of tricuspid and pulmonic BPVs, and comparison to mitral BPVs as these valves also continue to be better characterized.

Stephanie L. Sellers, MSc, PhD
Mark Hensey, MBBCh, BAO
Timothy R.G. Cartlidge, MD
Christopher T. Turner, PhD
Karen Lau, BSc
Althea Lai, BSc
Hannah Salcudean
Janarthanan Sathananthan, MBChB, MPH
Bruce M. McManus, MD, PhD
David J. Granville, PhD
Geoffrey W. Payne, PhD
Philippe Pibarot, PhD, DVM
John G. Webb, MD
David E. Newby, MD, PhD
Philipp Blanke, MD
Michael A. Seidman, MD, PhD
Marc R. Dweck, MBChB, PhD
Jonathon A. Leipsic, MD*

*Department of Radiology
St. Paul's Hospital
1081 Burrard Street
Vancouver, British Columbia V6Z 1Y6
Canada
E-mail: jleipsic@providencehealth.bc.ca
Twitter: @JonathonLeipsic

https://doi.org/10.1016/j.jcmg.2020.06.008

This work was supported by Edwards Lifesciences. Dr. Sellers is supported by fellowship from the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research. Dr. Turner is supported by fellowship from the Canadian Institutes of Health Research. Dr. Pibarot is supported by a Canadian Research Chair in Valvular Heart Disease. Dr. Newby is supported by the British Heart Foundation (CH/09/002, RE/13/3/30183, RG/16/10/32375) and is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA). Dr. Dweck is supported by the British Heart Foundation FS/14/78/31020 and is the recipient of the Sir Jules Thorn Award for Biomedical Research 2015. Dr. Leipsic is supported by a Canadian Research Chair in Advanced CardioPulmonary Imaging and the DeHann Award for Innovation in Cardiology. Drs. Blanke and Leipsic provide computed tomography core lab services for Edwards Lifesciences, Medtronic, Neovasc, Aegis, and Tendyne Holdings for which no direct compensation is received. Dr. Leipsic has stock options in HeartFlow Inc and Circl CVI; and is a consultant to Edwards Lifesciences. Dr. Pibarot provides echocardiology core lab services for Edwards Lifesciences and Medtronic for which no direct compensation is received. Dr. Webb is a consultant to Edwards Lifesciences, Abbott, and Vivitro Labs Inc. Dr. Sathananthan is a consultant to Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Philippe Pibarot, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Hirata K, Tengan T, Wake M, et al. Bioprosthetic tricuspid valve stenosis: a case series. Eur Heart J Case Rep 2019;3:ytz110.

2. Shetty R, Pibarot P, Audet A, et al. Lipid-mediated inflammation and degeneration of bioprosthetic heart valves. Eur J Clin Invest 2009;39:471–80.

3. Sellers SL, Turner CT, Sathananthan J, et al. Transcatheter aortic heart valves: histological analysis providing insight to leaflet thickening and structural valve degeneration. J Am Coll Cardiol Img 2019;12:135–45.

4. Cartlidge TRG, Doris MK, Sellers SL, et al. Detection and prediction of bioprosthetic aortic valve degeneration. J Am Coll Cardiol 2019;73:1107–19.

5. Torre M, Hwang DH, Padera RF, Mitchell RN, VanderLaan PA. Osseous and chondromatous metaplasia in calcific aortic valve stenosis. Cardiovasc Pathol 2016;25:18–24.

Temporal Trends in Detection and Outcomes of Low-Flow and Low-Gradient Aortic Stenosis

Aortic stenosis (AS) is the most common valvulopathy in the elderly (1). Low-flow (LF), low-gradient (LG) aortic stenosis (LFLG-AS) is an increasingly recognized clinical entity (2). We examined temporal trends and mortality in patients with LFLG-AS in a single-center, retrospective analysis of 25,507 consecutive transthoracic echocardiograms between January 2013 and July 2019 divided into quintiles of

time. Patients with severe AS, defined as aortic valve area <1 cm^2, were included. LG was defined as mean transvalvular pressure gradient <40 mm Hg, and LF was defined as stroke volume index <35 ml/m^2 or cardiac index <3 $l/min/m^2$. LFLG cases were classified into classical (reduced left ventricular ejection fraction <50%) and paradoxical (preserved left ventricular ejection fraction ≥50%) AS subtypes (1,2). This study was approved by the Melbourne Health Human Research Ethics Committee and the Western Health Office for Research. Multivariable logistic regression was used to analyze temporal trends in proportions of LFLG-AS over time while controlling for changes in risk factors. Kaplan-Meier survival curves were compared between AS subtypes and time quintiles using the log-rank test. Hazard ratios were determined by multivariable Cox regression analysis adjusted to age, sex, and body mass index.

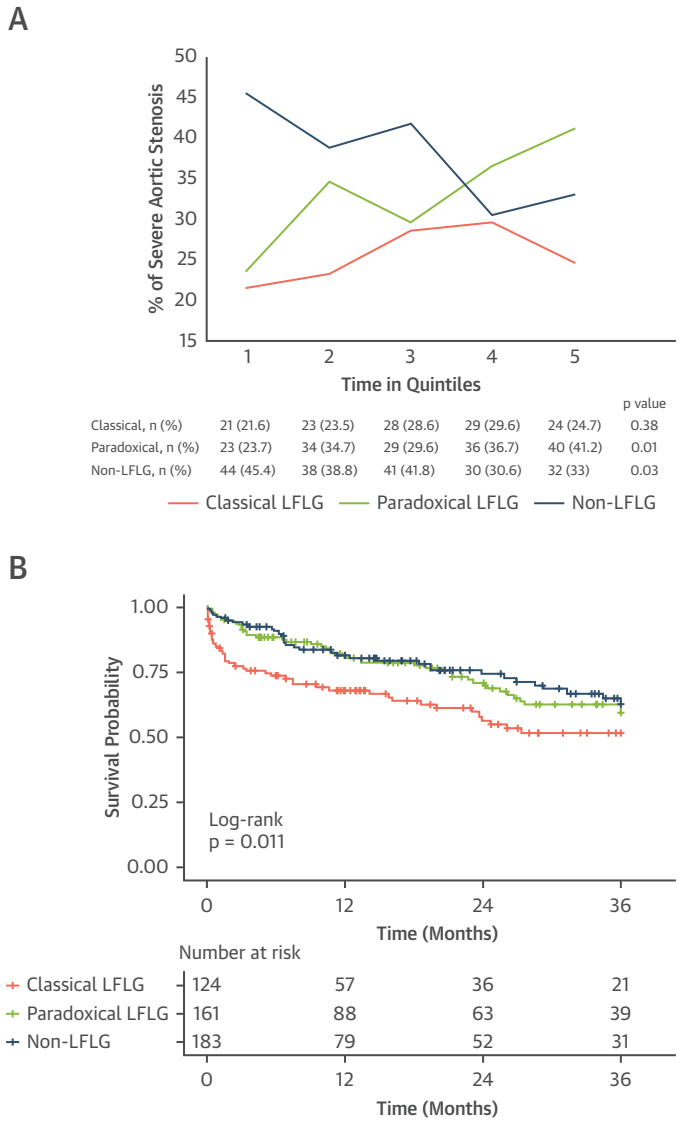
Among 488 patients with severe AS, 287 had LFLG-AS (125 with classical, 162 with paradoxical), 96 had LF and high gradient, and 38 had normal flow and LG. Over time, the diagnosis of paradoxical LFLG-AS increased ($p = 0.01$), non-LFLG-AS decreased ($p = 0.03$), and classical LFLG-AS remained stable (**Figure 1A**). The mean age increased from 77 to 79 years ($p = 0.04$), and the proportion of patients at least 70 years of age also increased over the study period from 74% to 83%, which correlated with trends of paradoxical LFLG.

Analysis of the temporal trend of the frequency of paradoxical LFLG-AS over the study period showed that increases in paradoxical LFLG were seen in females ($p = 0.02$) and in the absence of moderate or severe tricuspid regurgitation ($p = 0.02$), but not in males or patients with tricuspid regurgitation. Other univariable subgroup analyses found no significant change in frequency of paradoxical LFLG-AS over time according to age category, obesity, E/e′, atrial fibrillation, mitral regurgitation, and left ventricular hypertrophy. Multivariable logistic regression analysis also demonstrated no significant change in the frequency of paradoxical LFLG-AS after adjustment for age, obesity, E/e′ ratio, atrial fibrillation, moderate or severe mitral regurgitation, or left ventricular hypertrophy, implying that changes in these characteristics were responsible.

Among the 484 (99%) with follow-up information, there were 142 deaths (30.3%) over a median follow-up of 11.3 months (interquartile range: 1 to 29 months), and survival did not change significantly over time ($p = 0.20$). Survival was lowest in classical LFLG-AS patients ($p = 0.01$) (**Figure 1B**), among whom mortality was 43% (53 of 124), compared with 30% (48 of 161) in paradoxical LFLG-AS, and 22% (41 of 183) in non-LFLG-AS, respectively. Hazard ratio adjusted for age, sex, and body mass index for classical LFLG-AS was 2.02 (95% confidence interval: 1.27 to 3.20; $p = 0.003$) when compared with non-LFLG-AS.

Our study is the first to our knowledge to report an increasing frequency of paradoxical LFLG-AS at a hospital without onsite cardiac surgery, which we think avoids referral bias and reflects the frequency of this phenotype in the community. This trend was

FIGURE 1 Changes of Different AS Phenotypes Over Time and Survival Associated With AS Phenotypes



(A) Subtypes of aortic stenosis (AS) over time; **(B)** Kaplan-Meier survival curves for patients with classical, paradoxical, or non-LFLG AS. *Chi-square test for trend in proportions. LFLG = low-flow, low-gradient.

driven by risk factors that contribute to LFLG-AS, rather than by increased recognition. Mortality did not change over time and was similar in paradoxical LFLG-AS versus non-LFLG-AS but was highest in classical LFLG-AS.

Jonathan Sen, MBBS, BHSc
Thomas Manning, MBBS
Kyra Innes-Jones, MBBS
Christopher Neil, MBBS, PhD
Thomas H. Marwick, MBBS, PhD, MPH*

*Baker Heart and Diabetes Institute
75 Commercial Road
Melbourne, Victoria 3004
Australia
E-mail: tom.marwick@baker.edu.au

https://doi.org/10.1016/j.jcmg.2020.06.012

This work has been supported in part by a Partnership grant (1149692) from the National Health and Medical Research Council, Canberra. Dr. Sen was supported by scholarships from the National Heart Foundation of Australia (ID: 102578), National Health and Medical Research Council of Australia (ID: 1191044), and the Australian Government Research Training Program. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Philippe Pibarot, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

LGE for Risk Stratification in Primary Prevention in Children With HCM

Sudden cardiac death is the most visible, devastating, and unpredictable consequence of hypertrophic cardiomyopathy (HCM) in young patients (1). The recommended risk stratification approaches for childhood HCM have remained largely unchanged for more than 2 decades, with the treatment relying on the traditional HCM risk factors (2,3). Recently, Norrish et al. (4) proposed an individualized risk score for children determined by a predictive mathematical algorithm that uses 5 pre-selected continuous and qualitative indices. We designed a single-center study to compare the traditional American College of Cardiology Foundation/American Heart Association (ACC/AHA) algorithm with the novel HCM Risk-Kids score for our cohort, and investigated the effectiveness of cardiovascular magnetic resonance-derived fibrosis assessment for improving the performance of these models for identifying HCM children with endpoints.

We followed up on pediatric patients with HCM <18 years of age, with the echocardiographic evidence of left ventricular (LV) hypertrophy defined as LV diastolic wall thickness z-score of >2 (5), and the absence of hemodynamic conditions that could account for the observed hypertrophy. We collected relevant data on the patients regarding demographics, clinical symptoms, family history, and test results. Cardiovascular magnetic resonance (CMR) scan was performed using a 1.5-T scanner (Sonata and Avanto fit, Siemens, Germany). The presence of LV late gadolinium enhancement (LGE) was initially visually assessed by 2 independent experienced observers (J.P.M., L.M.). If positive, quantification was performed using the QMass v7.6 software (Medis, Leiden, the Netherlands) with a signal intensity threshold of >6 SD above the remote myocardium (>6 SD LGE). The extent of LGE was presented as a percentage of the total LV mass. The study was approved by the Bioethics Committee at the Children's Memorial Health Institute, and informed consent was obtained from the individual study participants and their parents. The endpoint was defined as cardiac death, resuscitated cardiac arrest, ventricular tachyarrhythmia, or appropriate implantable cardioverter-defibrillator discharge.

From the total of 90 patients with HCM recruited, we excluded 12 patients with phenocopies of sarcomeric HCM. The analyses considered 78 children (mean age 12.9 ± 3.8 years, 66% male, and mean body surface area 1.5 ± 0.4 m^2). They were followed prospectively (median follow-up period of 5.2 years, range 10 days to 9.3 years). Overall, 11 of the children (14.1%) reached a composite endpoint at a mean age of 13.7 years (range 1 to 21 years). We observed satisfactory endpoint identification performances of the considered models, namely, ACC/AHA (area under the curve [AUC]: 0.619, 95% confidence interval [CI]: 0.495 to 0.720), HCM Risk-Kids ≥4% (AUC: 0.771, 95% CI: 0.662 to 0.858), and HCM Risk-Kids ≥6% (AUC: 0.677, 95% CI: 0.562 to 0.779). Binary LGE improved the performances of ACC/AHA ($p < 0.01$), HCM Risk-Kids ≥4% ($p = 0.02$), and HCM Risk-Kids ≥6% ($p = 0.01$) models (**Figure 1**). Quantitatively measured LGE also improved ACC/AHA (AUC: 0.796, 95% CI: 0.690 to 0.879; DeLong $p < 0.01$) and HCM Risk-Kids ≥4% (AUC: 0.862, 95% CI: 0.765 to 0.929; DeLong $p = 0.03$). Further, HCM Risk-Kids ≥4% performed better than ACC/AHA at the baseline (DeLong $p < 0.01$) and with the application of both binary (DeLong $p < 0.01$) and quantitative (DeLong $p = 0.02$) LGE.