Physiologic Compensation Is Supranormal in Compensated Aortic Stenosis: Does it Return to Normal After Aortic Valve Replacement or Is it Blunted by Coexistent Coronary Artery Disease?

An Intramyocardial Magnetic Resonance Imaging Study

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Background—In compensated aortic stenosis (AS), cardiac performance measured at the ventricular chamber is typically supranormal, whereas measurements at the myocardium are often impaired. We investigated intramyocardial mechanics after aortic valve replacement (AVR) and the effects relative to the presence or absence of coronary artery disease (CAD+ or CAD−), respectively.

Methods and Results—Twenty-nine patients (46 to 91 years, 10 female) with late but not decompensated AS underwent cardiovascular MRI before AVR (PRE), with follow-up at 6 ± 1 (EARLY) and 13 ± 2 months (LATE) to determine radiofrequency tissue-tagged left ventricle (LV) transmural circumferential strain, torsion, structure, and function. At the myocardial level, concentric LV hypertrophy regressed 18% LATE (93 ± 22 versus 77 ± 17 g/m²; P < 0.0001), whereas at the LV chamber level, ejection fraction was supranormal PRE, 67 ± 6% (ranging as high as 83%) decreasing to 59 ± 6% LATE (P < 0.05), representing not dysfunction but a return to more normal LV physiology. Between the CAD+ and CAD− groups, intramyocardial strain was similar PRE (19 ± 10 versus 20 ± 10) but different LATE, with dichotomization specifically related to the CAD state. In the CAD− patients, strain increased to 23 ± 10% (+20%), whereas in CAD+ patients it fell to 16 ± 11% (−26%), representing a nearly 50% decline after AVR (P < 0.05). This was particularly evident at the apex, where CAD− strain LATE improved 17%, whereas for CAD+ it decreased 2.5-fold. Transmural strain and myocardial torsion followed a similar pattern, critically dependent on CAD. AVR impacted LV geometry and mitral apparatus, resulting in decreased mitral regurgitation, negating the double valve consideration.

Conclusions—In AS patients after AVR, reverse remodeling of the supranormal systolic function parallels improvement in cardiovascular MRI-derived regression of LV hypertrophy and LV intramyocardial strain. However, discordant effects are evident after AVR, driven by CAD status, suggesting that the typical AVR benefits are experienced disproportionately by those without CAD and not by those obliged to undergo concomitant coronary artery bypass grafting/AVR. (Circulation. 2005;112[suppl 1]:I-429–I-436.)

Key Words: aortic stenosis ■ aortic valve replacement ■ intramyocardial strain ■ CAD ■ MRI

Many mechanisms of systolic and diastolic left ventricular (LV) dysfunction are well described in advanced aortic stenosis (AS).1–10 Despite this, there are compelling data to suggest that even in the presence of preserved or supranormal chamber function, innate myocardial performance may be severely dysfunctional in AS patients. Specifically, LV hypertrophy (LVH) resulting from compensatory hypertrophy of each sarcomere can achieve increased ejection performance at the chamber level despite decreased intrinsic function.11,12 One can extrapolate from other pathological entities where LVH has been proven to be an adverse prognostic marker, such as hypertrophic cardiomyopathy,13...
hypertension, and congenital heart disease, that a similar relationship likely exists in AS patients.

Coexistent epicardial ischemic heart disease may also alter the response of LV mechanics to aortic valve replacement (AVR). Importantly, the presence of coronary artery disease (CAD) may blunt the expected beneficial improvements in LV mass regression and mechanics after surgical relief of abnormal afterload because of AS. To date, despite the common occurrence of patients with both CAD and AS, there are no data that directly support this hypothesis.

Assessment of Myocardial Function in LVH

In patients with AS, the increased LV mass permits supranormalization of stress, facilitating supranormal mechanical function at the chamber level, in the presence of underperforming sarcomeres. Measurements of intramyocardial deformation using echocardiographic midwall shortening (MWS) show that contractile function is impaired. However, in the calculation of MWS, there are mathematical assumptions that may not always be met, whereas invasive techniques, such as tantalum markers or piezoelectric crystals, are not available for use in patients. Cardiovascular magnetic resonance (CMR) radiofrequency (RF) tissue-tagging technique uses selective saturation and modulation of myocardial signal in a transmural and noninvasive fashion. As the heart contracts, tracking of saturation grids throughout the cardiac cycle yield direct measurements of myocardial deformation. The resulting deformation patterns give the appearance of a deforming lattice attached to the myocardium. These deformations are described mathematically using units of strain (%S). CMR tissue tagging has been shown to be reproducible and suitable for applications when detailed interrogation of myocardial mechanics is required.

Quantitative imaging has been performed evaluating the role of chamber function [ejection fraction (EF)] by imaging in AS, but there are no studies to quantitate systolic intramyocardial function using circumferential or radial strain specifically for AVR patients with CAD. Only very limited studies of systole and diastole using torsional indices are available. Because many patients with AS exist (estimated at 3,000,000), additional understanding of intramyocardial mechanics in AS is required. Furthermore, the effects of surgical replacement of the aortic valve on LV structural and mechanical properties are not well understood. This knowledge will impact our downstream understanding of the effects of AVR surgery, the probable disparate effects on those with and without CAD, and potentially aid the upstream timing of AVR, especially as it related to those with CAD.

The current study was performed to test the following hypotheses: (1) patients with advanced but compensated AS have normal or supranormal function measured at the chamber level but have abnormal myocardial function as assessed by CMR-derived intramyocardial strain, and that process will reverse on correction of the abnormal afterload by AVR; (2) in patients with CAD, there will be blunting of the return to normal myocardial function after AVR as compared with those without CAD; and (3) AVR may impart beneficial LV reverse-remodeling that impacts mitral regurgitation (MR).

Methods

Population

Patients referred for AVR were enrolled after Institutional Review Board approval and obtained signed consent. All of the patients were identified via standard clinical metrics independent of CMR evaluation. To provide homogeneity in the pathology of AS, patients were excluded if there was aortic or MR assessed by echocardiographic imaging greater than moderate (>$2+$), mitral stenosis, prior valve replacement, myocardial infarction, history of hypertension, coronary artery bypass grafting (CABG), or angioplasty. Specific contraindications to CMR were the presence of a pacemaker, defibrillator, history of metal fragments, implants, cerebrovascular clips, or claustrophobia.

CMR Imaging

Using a General Electric Signa 1.5T CV/i cardiac-triggered CMR system with a 40 mT/m maximum gradient strength and 150 mT/m/ms maximum slew rate, scout images were obtained to plan double-oblique views in the 2- and 4-chamber views from which short-axis contiguous 7-mm slices traversing the mitral valve plane through LV apex were acquired using a steady-state free precession (FIESTA) cine sequence with a field of view of 38 cm², matrix of 256×192, and flip angle of 45°. The temporal resolution was 30±5 ms, repetition time of 3.7 ms, echo time of 2.2 ms, 100% phase field of view, and 0.75 number of excitations. From the short-axis images, LV end-diastolic volume, LV end-systolic volume, LV stroke volume, LV EF, and LV mass were measured and indexed to body surface area. LV mass was derived via Simpson’s method multiplied by the specific gravity of myocardium (1.055 g/mL).

RF intramyocardial tissue-tagging was performed using a cine sequence (FastCard) with similar parameters incorporating a 7-mm slice with deposition of orthogonal tags at an intratag stripe distance of 7 mm (Figure 1). Contiguous short axis slices were obtained throughout the entire LV with a temporal resolution of 33±5 ms.
Analysis of the RF tissue-tagging was performed assuming local homogeneous myocardial material properties between tag vertices computed to yield local measurements of 1D circumferential strain (%S) for endocardial, midwall, and epicardial segments; data from individual slices were combined to calculate the %S for the base, mid, and apex.

From the tissue-tagged images, LV torsion (degrees) was derived from base to apex by measuring the angular rotation relative to the centroid, using HARP software (Diagnosoft; requiring 60 to 75 minutes for strain and 35 to 45 minutes for torsion/untwisting per patient analysis). Torsion was referenced to the base for 16 midwall segments equally positioned around each short axis slice. Torsion work was defined as total LV torsion integrated over systolic ejection time.

Phase velocity mapping was used to quantify 3D peak and mean aortic transvalvar gradients. Velocity encoding was set at 350 to 550 cm/s with encoding in x, y, and z directions. Phase velocity mapping was resolved into 60 phases/cardiac cycle achieving high-temporal resolution (19.3 ms).

All of the images were analyzed offline on a semiautomatic MASS Plus flow program (Medis). CMR imaging was performed (5±3 days) before AVR (PRE), at 6±1 months (EARLY), and at 13±2 months (LATE). The mean imaging time for the patients was 56±14 minutes.

Statistics
Continuous variables were reported as mean ± 1 SD. Categorical variables were reported as percentages with 95% CIs. Comparisons of PRE to EARLY/LATE were performed by the paired t test. Effects across groups were analyzed using 1-way ANOVA, and repeated-measures ANOVA was performed for comparisons over time. Statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS, Inc.). All of the statistical comparisons were performed using 2-tailed significance tests with P<0.05 considered statistically significant.

Results
Twenty-nine patients (mean, 76 years; range, 46 to 91 years; 10 women) with severe but compensated AS underwent CMR at the PRE time point. No patient was New York Heart Association IV, and all were able to perform the daily activities of living without undue fatigue. No patient had manifested syncope in the 3 months before AVR. No patient had insulin-dependent diabetes mellitus; 4 had noninsulin-dependent diabetes mellitus, 2 were CAD−, and 2 were CAD+.

The peak and mean aortic transvalvar velocities by CMR were 5.4±0.9 and 3.3±1.4 m/s, respectively, representing 118±3 and 45±6 mm Hg gradients. All of the patients had an EF >45%, with the majority (83%) >55% ranging to 83% (Table 1).

After AVR, CMR examinations were performed at 6±1 months (EARLY) and 13±2 months (LATE) (Figure 1). Twenty-four patients (83%) returned after AVR, forming the following study group: 1 death at day 5 from reexpansion pulmonary edema, 1 pacemaker insertion, 2 patients refused follow-up, and 1 lost to follow-up. Seven patients (30%) had CAD (CAD+) defined by the presence of ≥1 vessel with a lesion by catheterization >50% stenosis or receiving a CABG to the respective vessel. The average number of CABG grafts was 2.3±0.9, including 85% left internal mammary grafts. Seventeen patients (70%) had no lesions by cardiac catheterization and received no CABG (CAD−). Both antegrade and retrograde blood cardioplegia was used as the only myocardial preservative. A prosthetic valve was placed in most patients (St. Jude, 83%, and Toronto Freestyle-SPV, 17%). No significant bias in the placement of the prosthetic size was present (20.3±1.4 mm versus 19.6±1.9 mm, respectively, for CAD+ versus CAD−) (Fig-
No patient had perioperative or postoperative decline in EF or gradients. Additionally, the TEE (and CMR) confirmed that thesis placement and integrity with acceptable transvalvar esophageal echocardiography (TEE) to assure proper pros-

equivocal as sharper declines in EF EARLY (P<0.05), with little improvement noted in CAD- patients. In both groups, the end-
diastolic volume index and end systolic volume index re-
mained mildly dilated compared with historic controls.

At the level of the myocardium, as expected, concentric LVH was noted PRE, with the CMR-measured left ventric-
ular mass index being 93 ±22 g/m². After AVR, LVH rapidly declined by 8%, whereas in the 6 patients with the lowest EF (45% to 55%), the EF increased by 8%.

All of the CAD+ patients had an EF >55% PRE, and this state was maintained through the LATE time point. No relationship was noted with regard to the degree or temporal changes of EF in CAD+ patients throughout the study with respect to the number of grafts, number of patients with left internal mammary grafts (6 of 7 patients), cross-clamp time, or valve prosthesis. For all of the patients, the left ventricular end diastolic volume index was unchanged at the PRE through the LATE time points. At the PRE through the LATE time points, the LV chamber tended to be larger in CAD− compared with CAD+ patients. In both groups, the end-
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TABLE 3. Transmural Circumferential Strain (%S) PRE to LATE (13±2 Months) After AVR

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAD− (573 Myocardial Segments)</th>
<th>CAD+ (128 Myocardial Segments)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>LATE</td>
</tr>
<tr>
<td>BASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>23±10</td>
<td>26±8</td>
</tr>
<tr>
<td>Mid</td>
<td>18±8</td>
<td>19±6</td>
</tr>
<tr>
<td>Epi</td>
<td>15±9</td>
<td>15±8</td>
</tr>
<tr>
<td>MID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>24±10</td>
<td>29±8</td>
</tr>
<tr>
<td>Mid</td>
<td>18±7</td>
<td>21±6</td>
</tr>
<tr>
<td>Epi</td>
<td>16±9</td>
<td>17±8</td>
</tr>
<tr>
<td>APEX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>26±11</td>
<td>30±9</td>
</tr>
<tr>
<td>Mid</td>
<td>17±9</td>
<td>20±9</td>
</tr>
<tr>
<td>Epi</td>
<td>16±9</td>
<td>19±9</td>
</tr>
</tbody>
</table>

Endo indicates endocardial; Mid, midwall; Epi, epicardial.

which was similar for CAD− and CAD+ patients (19±10 versus 20±10%, respectively). LATE strain increased to 22±9% (±15%) for the group (P<0.001). However, in CAD− patients, %S increased to 23±10% (+20%), whereas it decreased to 16±11% for CAD+ patients (−26%; P<0.05 for both). Thus, after AVR, the CAD+ patients experienced a nearly 50% decrease in myocardial strain relative to CAD− patients.

When examining strain patterns from base to apex, a gradient was noted in both CAD− and CAD+ patients. In CAD− patients, the improvement LATE was greatest at the apex (17%), whereas in CAD+ patients, loss of function was most severe at the apex (−41%; P<0.001) (Table 3). Similarly, for CAD− patients, the basal strain increased the least (6%; P<0.04) at the LATE time point, but was unchanged for CAD+ (P value was not significant) (Table 3). When examined transmurally, intramyocardial strain improved PRE to LATE in CAD− patients, with a transmural gradient noted (lowest toward the epicardium, and increased progressively as the apex was approached (Tables 3 and 4). In contrast, in CAD+ patients, strain decreased PRE to LATE (P<0.001) (Figure 3).

At the LATE time point, 17 patients had torsion and rotation data available. As noted above, at the level of the LV cavity, EF was typically supranormal. Similarly, at the PRE time point, torsion was markedly elevated 16.6±7.2° (range, 12° to 46°) and remained so at the EARLY time point (16.3±14.3°) but normalized by the LATE time point (9.0±3.4°; P<0.05) compared with historic controls (10±3°) (Figures 4 and 5). However, the rate of torsion generation (°/mm/ms) was unchanged PRE to LATE (0.074±0.031°/ms versus 0.065±0.031°/ms; P value was not significant). Maximum torsion was realized at the apex and was essentially linear from base to apex (P<0.001), although it was subdued in CAD+ patients (Table 2).

The torsion work regressed by 35% EARLY, additionally decreasing by 15% LATE (P<0.001 for temporal pattern; 10.7±6.8 versus 6.9±4.7 °/mm/ms; P<0.05). The LVMI was positively correlated with the time to generate 50% maximal absolute torsion PRE (r=0.63), EARLY (r=0.40), and LATE (r=0.89; P<0.005).

MR frequently accompanies severe AS, thus, in patients undergoing AVR, there is often ambiguity as to whether a single or double valve replacement surgery should be performed. The extent and grade of MR was semiquantitatively determined by CMR criteria using FIESTA cine images (noting that separate echocardiography criteria were used for patient inclusion criteria, whereas CMR data were used for analysis). Valve geometry (tenting angle, area, and annular dimension) and LV sphericity index were measured. At the PRE time point, the range and grade of CMR-measured MR was trace through 4+ (severe) with a mean of 2+ (moderate). The grade of MR decreased in 92%, was unchanged in 4%, and increased 1 grade in 4% (i.e., in 1 patient who had the least LV remodeling EARLY). The mean decrease in MR for the
group was 1.5 grades to trace-1+ (mild). No patient required a double valve replacement throughout the study. At the LATE time point, the LV sphericity improved compared with PRE (2.05 ± 0.3 versus 2.23 ± 0.3; \( P < 0.05 \)). There was a correlation between improvement in MR grade and 2 valvular parameters: annular dimension and tenting angle (\( r = 0.59; \ P < 0.01 \)). Surprisingly, there was no correlation of degree of MR with PRE or EARLY aortic transvalvar gradients measured by CMR or perioperative TEE or with the extent of coexistent CAD.

Discussion
Progressive concentric hypertrophy in patients with AS has deleterious physiological and clinical effects. Although the compensatory response to increased afterload, an increase in force-generating sarcomeres, is initially beneficial, incipient pathologic LVH leads to adverse long-term effects on LV contractile function. Replacement of the stenotic aortic valve reduces afterload, ideally leading to reversal of the hypertrophic process. The adequacy of LVH regression directly affects the reinstatement of normal LV volumetrics, mechanics, and pump function. Conventionally, these parameters are judged before and after AVR using measurements confined predominantly to chamber function, such as EF and shortening fraction. This approach, although traditionally helpful in many cardiac pathologies, may be misleading in patients with advanced but compensated AS. Specifically, concentric LVH via the parallel addition of myocytes allows normal or supranormal ejection performance at the chamber level, mostly for geometric reasons, despite decreased shortening at the fiber level. A diagnostic technique, such as CMR, that can noninvasively directly assess myocardial properties (in addition to chamber properties, such as EF), therefore, has clinical merit. Notably, there is a very well-established population benefit that ensues after AVR, returning survival curves to age-predicted actuarials but without regard to CAD status. Here we show, however, that the influence of CAD blunts the expected myocardial benefit of AVR via the CMR technique.

LV Structure and Function PRE, EARLY, and LATE
In patients with compensated AS, before AVR, CMR analysis showed that the LV was mildly dilated with moderate concentric hypertrophy, whereas the chamber often exhibited supranormal systolic function. In sharp contrast, CMR intramyocardial circumferential strain measured by intramyocardial tissue-tagging was shown to be depressed compared with normals. This dysfunction was offset by an augmentation of LV torsion, which occasionally exceeded 40°. At the EARLY time point, little change was observed in LV dilation, but there was continued regression of LVH with a corresponding decrease in EF, representing a return toward but not reaching the normal uncompensated state. After AVR, the processes reversed; that is, intramyocardial function improved, whereas torsion, no longer necessary at supraphysiologic levels, decreased in relation to LV mass regression. This process continued, albeit at a slower pace up to the LATE time point, where an additional reduction of LVH, EF, and torsion occurred with a matched increase in intramyocardial performance.

Impact of CAD on LV Structure and Function
Previously, the impact of CAD on either the correction or perturbation of AS by AVR had not been evaluated. However, as the age of patients eligible to receive AVR increases, the incidence of concomitant CAD is expected to increase. Importantly, our population was specifically screened to be devoid of the influences of hypertension to avoid a confound-
ing influence on LV mass regression and baseline LV geometry that had been reported previously. When compared with AS patients with CAD (CAD+), baseline LV volumes tended to be smaller but with thicker walls resulting in a 15% increase in LV mass. This LVH contributed to a trend of increased chamber function by EF (3%) but without a difference in LV strain between groups PRE. After AVR in CAD+ patients, LVH regressed more slowly over time, whereas intramyocardial mechanical performance became markedly depressed as compared with CAD− patients, globally averaging nearly 50% lower with a 2.5-fold decrease noted at the apex. This pattern held for the EARLY and LATE time points. There was no prediction of strain perturbations using multivariate analysis with the number of bypasses performed, cross-clamp time, luminal severity, left main disease, or intubation time. We infer that the presence of CAD is sufficient to retard LV mass regression via a number of putative pathways, notably, an inability to reset mRNA signaling and failure to inactivate metalloproteinases promoting interstitial fibrosis and blunting its resorption after AVR. However, exogenous mechanisms for these observations need to be additionally considered. Taken together, the consideration of CMR analyses may lead to a reconsideration of the timing of AVR in those with concomitant CAD. This study demonstrated no difference in PRE circumferential strain between CAD− and CAD+ patients (19 ± 10 versus 20 ± 10%;$^2$) thus, in CAD+ patients presenting with 1 SD below “normal” strain, that is, a strain of 10%;s, it would seem appropriate to consider surgical correction, with 15%$^2$s suggesting an expectant surgical management.

Other Clinical Implications

MR frequently accompanies severe AS often leading to clinical ambiguity when faced with possible double-valve replacement (because of the greater operative risk compared with a single prosthesis). This CMR investigation demonstrated that in >90% of patients, MR improved by >1 grade after AVR. Interestingly, no predictive relationship was found for the decline in MR using parameters such as EF, transvalvar gradient, or LV mass. However, by linear regression, the LV sphericity index and mitral geometry (tenting angle and annular area) were correlated with improvement in MR grade ($r=0.59; P<0.01$). In this study, the sole patient in whom MR slightly worsened had the worst preoperative sphericity index. No patient required a double-valve perioperatively or through follow-up.

Although there was a difference in the age of the groups just meeting statistical significance, LV ejection performance has been shown to increase, not decrease, with age via both echocardiographic$^{23}$ and CMR$^{24}$ strain and EF measurements of MWS and EF, as well as CMR$^{24}$ strain and EF. Indeed, the EFs were similar in our study, whereas the 2D strain measurements were nearly superimposable, likely discounting an age-related effect to our findings.

Cardiovascular MRI provides a wealth of data pertinent to the disease process of AS, allowing unmasking of the paradox of chamber function versus myocardial contractile performance.$^{25}$ Presently, the impact of CMR on more precise surgical timing remains to be determined. Torsion derived from CMR images was shown to regress following a temporal pattern, which may be related to relatively early abolition of mRNA signaling after AVR compared with tardy signaling of metalloproteinase inhibition$^6$ such that, by 1 year, the lusitropic dysfunction measured by markedly delayed untwisting had normalized (Figure 4), revealing an additional benefit to AVR.

Clinical issues requiring clarification condense around the concept formulated by Lorell and Carabello,$^{26}$ that is, “exuberant LVH” noted in women, particularly the elderly, who display a marked propensity for LVH compared with their male counterparts.$^{27}$ It follows that women with an exaggerated LVH pattern relative to men may have an attenuated regression in LVH after AVR, which translates into additional altered LV structure, function, and intramyocardial indices. This issue and others are addressable using CMR, and we continue to accumulate data to address them.

Acknowledgments

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