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Coronary Physiology During Exercise and Vasodilation in the Healthy Heart and in Severe Aortic Stenosis

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ABSTRACT

BACKGROUND Severe aortic stenosis (AS) can manifest as exertional angina even in the presence of unobstructed coronary arteries.

OBJECTIVES The authors describe coronary physiological changes during exercise and hyperemia in the healthy heart and in patients with severe AS.

METHODS Simultaneous intracoronary pressure and flow velocity recordings were made in unobstructed coronary arteries of 22 patients with severe AS (mean effective orifice area 0.7 cm^2) and 38 controls, at rest, during supine bicycle exercise, and during hyperemia. Stress echocardiography was performed to estimate myocardial work. Wave intensity analysis was used to quantify waves that accelerate and decelerate coronary blood flow (CBF).

RESULTS Despite a greater myocardial workload in AS patients compared with controls at rest (12,721 vs. 9,707 mm Hg/min^{-1}; $p = 0.003$) and during exercise (27,467 vs. 20,841 mm Hg/min^{-1}; $p = 0.02$), CBF was similar in both groups. Hyperemic CBF was less in AS compared with controls (2,170 vs. 2,716 cm/min^{-1}; $p = 0.05$). Diastolic time fraction was greater in AS compared with controls, but minimum microvascular resistance was similar. With exercise and hyperemia, efficiency of perfusion improved in the healthy heart, demonstrated by an increase in the relative contribution of accelerating waves. By contrast, in AS, perfusion efficiency decreased due to augmentation of early systolic deceleration and an attenuated rise in systolic acceleration waves.

CONCLUSIONS Invasive coronary physiological evaluation can be safely performed during exercise and hyperemia in patients with severe aortic stenosis. Ischemia in AS is not related to microvascular disease; rather, it is driven by abnormal cardiac-coronary coupling. (J Am Coll Cardiol 2016;68:688–97) © 2016 by the American College of Cardiology Foundation.

Patients with severe aortic stenosis (AS) and unobstructed coronary arteries have a reduced coronary flow reserve (CFR) (1,2), often accompanied by angina during exercise, and an increased risk of myocardial infarction during noncardiac surgery (3). Although the precise mechanisms are yet to be elucidated, recent developments have paved the way for a novel approach to studying these phenomena. First, it is now possible to carry out detailed invasive coronary evaluation in humans during exercise (4). Second, the technique of wave intensity analysis (WIA) provides a powerful tool to study the intimate

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relationship between cardiac contraction and coronary blood flow (CBF), often referred to as cardiac-coronary coupling. Coronary WIA provides directional, quantitative, and temporal information that has been used to study various human disease processes including left ventricular hypertrophy, the response to transcatheter aortic valve replacement (AVR), the response to pacing, the "warm-up angina" phenomenon, ventricular remodeling following an acute coronary syndrome, and cardiac resynchronization therapy (4–9). Interestingly, detailed invasive physiological testing and WIA have not previously been used to characterize the response of the healthy human heart to exercise or adenosine hyperemia.

SEE PAGE 698

In myocardial ischemia investigations, the heart is often subjected to stress to determine its ability to augment myocardial blood flow. The stressor can be physiological (exercise) or pharmacological (using agents such as adenosine). Although both forms of stress are chosen to enhance CBF, their influence on cardiac-coronary coupling may be profoundly different, especially in the diseased heart. The aim of this descriptive physiological study is 2-fold: to provide a detailed description of the changes in CBF and cardiac-coronary coupling in response to exercise compared with adenosine-induced hyperemia in the healthy heart; and to determine whether patients with severe symptomatic AS differ in their responses to these stressors.

METHODS

The index group comprised patients with severe symptomatic aortic stenosis (defined as an effective orifice area [EOA] <1 cm^2 or peak flow velocity [V_{max}] >4 ms^{-1}) being considered for surgical AVR. The control group comprised patients without AS, but with normal coronary angiograms, performed during the investigation of chest pain. Inclusion criteria were preserved left ventricular (LV) function (LV ejection fraction >50%) and unobstructed coronary arteries (no lesion >50% in diameter assessed visually). Exclusion criteria were concomitant valve disease (greater than mild on echocardiography), history of syncope, recent acute coronary syndrome or presentation with heart failure (within 4 weeks), or any comorbidity that may influence exercise tolerance. The study protocol was approved by the institutional research ethics committee.

PROTOCOLS. Catheterization was via the right radial artery using standard coronary catheters. All patients had aspirin (300 mg) and clopidogrel (600 mg) pre-loading, intra-arterial unfractionated heparin (70 U/kg), and intracoronary nitroglycerin before diagnostic angiography and intracoronary physiological measurements. A dual pressure and Doppler sensor-tipped 0.014-inch intracoronary wire (Combowire, Volcano Corp, San Diego, California) was used to measure coronary pressure and flow velocity. Wire pressure was first normalized to that recorded by the fluid-filled pressure manometer and the tip advanced into a distal left coronary artery and manipulated until a stable and optimal Doppler velocity trace was obtained. Hemodynamic measurements were taken under resting conditions and continuously during supine bicycle exercise.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVR = aortic valve replacement
CBF = coronary blood flow
CFR = coronary flow reserve
EOA = effective orifice area
LV = left ventricular
MR = microvascular resistance
MR_{dias} = diastolic microvascular resistance
RPP = rate pressure product
SBP = systolic blood pressure
WI = wave intensity
WIA = wave intensity analysis

After full recovery from exercise (return to baseline levels of heart rate, blood pressure, and average peak velocity), a second set of resting hemodynamic data was acquired (rest-2 period). Hyperemia was then induced with intravenous adenosine. All relative changes reported with hyperemia use rest-2 for baseline measurements.

A specially adapted supine cycle ergometer (ergosana, Bitz, Germany), which allowed a standardized incremental increase in workload, was attached to the catheter laboratory table. Exercise began at a workload of 30 W and incrementally increased every 2 min by 20 W. Where muscle weakness restricted the use of increasing workloads, resistance was fixed at the maximum tolerated level, and exercise continued until exhaustion.

Signals were sampled at 200 Hz, with the data exported into a custom-made study manager program (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands) and a minimum of 10 consecutive beats extracted for each condition. Pan-cardiac cycle analysis and WIA were performed on custom-made software, Cardiac Waves (Kings College London, London, United Kingdom). Savitzky-Golay filters were applied to preserve peaks in the data while smoothing (10). Ensemble averages of the selected cardiac cycles were performed. Microvascular resistance (MR) was calculated as the ratio of the distal mean coronary pressure (P_d) and the average peak velocity. The diastolic MR (MR_{dias}) was defined as the MR during mid-to-late diastole, where myocardial compressive forces are at their lowest (11). Measuring MR in this interval gives insight into the vascular component of MR.

For the purposes of WIA, diastole onset was defined as the dichotic notch on the arterial pressure waveform. Net coronary wave intensity (dI) was

calculated as the product of time derivatives (dt) of ensemble-averaged coronary pressure and flow velocity (U) as follows: $dI = dP_d/dt.dU/dt$ (12). Net wave intensity (WI) was separated into forward and backward components.

For each patient, 4 dominant waves were identified and included in our analysis:

1. Early systolic deceleration: associated with CBF deceleration during isometric contraction (sometimes referred to as the backward compression wave).
2. Systolic acceleration: associated with peak aortic pressure and increasing CBF (sometimes referred to as the forward compression wave).
3. Late systolic deceleration: the fall in aortic pressure in late systole leads to CBF deceleration (sometimes referred to as the forward expansion or "suction" wave).
4. Diastolic acceleration: the rapid reduction of LV pressure leads to a fall in compression of intramyocardial vessels and acceleration of CBF (sometimes known as the backward expansion or "suction" wave).

We reported the magnitude of each wave (its peak WI). The absolute values of the 4 dominant waves were summed in both the AS and control group at rest, during peak exercise, and hyperemia; plus, the percentage of accelerating and decelerating WI was calculated.

Previous coronary WIA studies have demonstrated a wide variation in the magnitude of wave intensity between patients (8,13). This is in part related to inherent errors in measurement, but also likely reflects true population variation. We therefore calculated the percentage change in waves from rest to exercise and rest to hyperemia, thereby allowing each patient to act as their own control, helping to eliminate some of this inherent variation.

A subset of 13 patients with AS underwent bicycle stress echocardiography to quantify myocardial work by measuring the rate pressure product (RPP). All patients in the subset had a full resting transthoracic echocardiographic study followed by a bicycle stress echocardiogram. The exercise protocol used during the stress echocardiogram was identical to the protocol used in the catheterization laboratory. The RPP was defined as the product of heart rate and LV systolic blood pressure (SBP), which correlates with myocardial oxygen consumption (14). LV pressure was estimated from the sum of SBP and the transvalve pressure gradient after pressure recovery (15). In the control cohort, LV pressure was assumed to be equal to aortic pressure in systole; hence, the RPP was calculated as the product of heart rate and aortic systolic pressure.

TABLE 1 Patient Demographics

	Control (n = 38)	Aortic Stenosis (n = 22)	p Value
Male	28 (74)	18 (82)	0.54
Age, yrs	61 ± 10	69 ± 8	0.001
Hypertension	22 (58)	11 (50)	0.55
Diabetes mellitus	8 (21)	3 (14)	0.47
Hypercholesterolemia	27 (71)	14 (64)	0.55
Smokers	7 (18)	2 (9)	0.33

Values are n (%) or mean ± SD.

STATISTICAL ANALYSES. Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, New York). Normality of data was visually assessed (using histograms and the normal Q-Q plot) and using the Shapiro-Wilk test. Continuous and normal data are expressed as mean ± SD and compared using paired or unpaired Student *t* tests as appropriate. Non-normal continuous data are expressed as median with interquartile range and compared using the Mann-Whitney *U* test or Wilcoxon signed rank test as appropriate. A 2-tailed test for significance was performed for all analyses; $p \leq 0.05$ was considered statistically significant. Correlation was assessed with the Pearson correlation coefficient. No adjustments are made for comparisons across multiple time points.

RESULTS

Sixty individuals were recruited into the study: 22 with AS and 38 healthy controls (Table 1). All AS patients and 17 consecutive patients in the control group performed supine bicycle exercise. Hyperemia was induced in 19 patients with AS and 30 controls.

The AS cohort all had severe symptomatic AS with a peak aortic valve gradient of 92 ± 26 mm Hg, V_{max} across the aortic valve of 4.7 ± 0.66 ms^{-1}, and an EOA of 0.74 ± 0.16 cm^2 (Table 2).

The exercise protocols in the cardiac catheterization and echocardiography laboratories were completed safely in patients with and without AS. There were no significant adverse effects of adenosine infusion in either group.

In response to exercise, heart rate and SBP increased and the diastolic time fraction decreased in AS patients as well as controls ($p < 0.001$ in both groups). There was a significant rise in diastolic blood pressure in AS, but not in controls. Induction of

TABLE 2 Echocardiographic Characteristics of Patients with Aortic Stenosis

V_{max}, ms^{-1}	4.70 ± 0.66
Mean aortic valve gradient, mm Hg	57 ± 16
Peak aortic valve gradient, mm Hg	92 ± 26
Effective orifice area, cm^2	0.74 ± 0.16
Ejection fraction, %	59 ± 5
Lateral S′, ms^{-1}	7.6 ± 2.0
E/E′	10 ± 3
Left atrial area, cm^2	25 ± 7
Left ventricular mass, g	221 ± 70

Values are mean ± SD.

E/E′ = ratio of mitral inflow velocity to velocity of the mitral valve annulus during passive left ventricular filling; lateral S′ = peak systolic velocity of the lateral mitral valve annulus; V_{max} = maximal velocity across the aortic valve.

hyperemia led to a rise in heart rate but a fall in SBP in both groups ($p < 0.001$). Diastolic blood pressure and diastolic time fraction did not change in AS but decreased in controls during hyperemia (Figure 1).

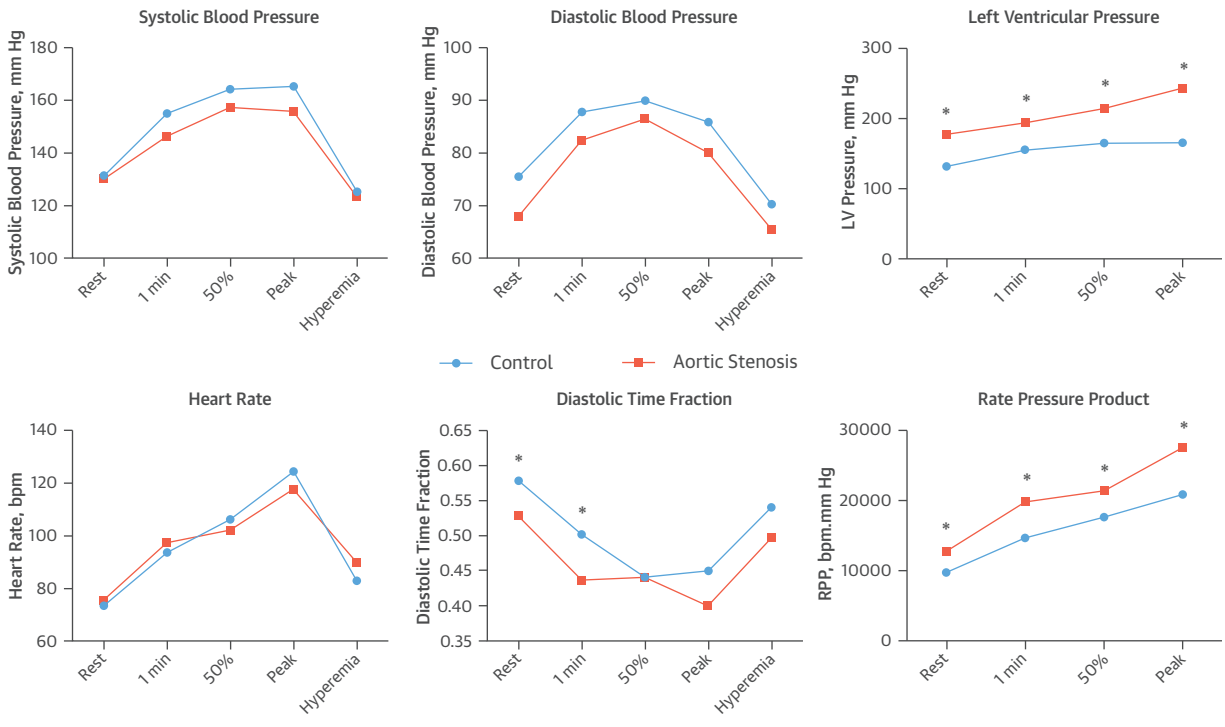
Average peak velocity increased during exercise in both groups ($p < 0.001$). Exercise CFR in AS and controls was similar (1.7 ± 0.6 vs. 1.7 ± 0.6, respectively; $p = 0.57$), but hyperemic CFR was less in AS patients (1.9 ± 0.7 vs. 2.5 ± 0.6, respectively; $p = 0.006$).

Microvascular resistance fell during exercise in both groups ($p < 0.001$). The relative change in MR on exercise was not different between AS and controls (0.8 ± 0.3 vs. 0.8 ± 0.3; $p = 0.70$; the closer the value is to 1, the smaller the reduction from baseline). At rest, MR_{dias} was lower in AS patients than controls (354 ± 172 mm $Hg/s^{-1}/m^{-1}$ vs. 480 ± 220 mm $Hg/s^{-1}/m^{-1}$; $p = 0.025$). With exercise, MR_{dias} dropped in both groups relative to baseline, and there was no between-group difference during exercise.

MR fell with hyperemia in both groups ($p < 0.001$) (Figure 2); though less so in AS patients (0.6 ± 0.3 vs. 0.4 ± 0.1; $p = 0.001$). There was no difference in MR during hyperemia between AS and controls. Full details of hemodynamic parameters are shown in Online Table 1.

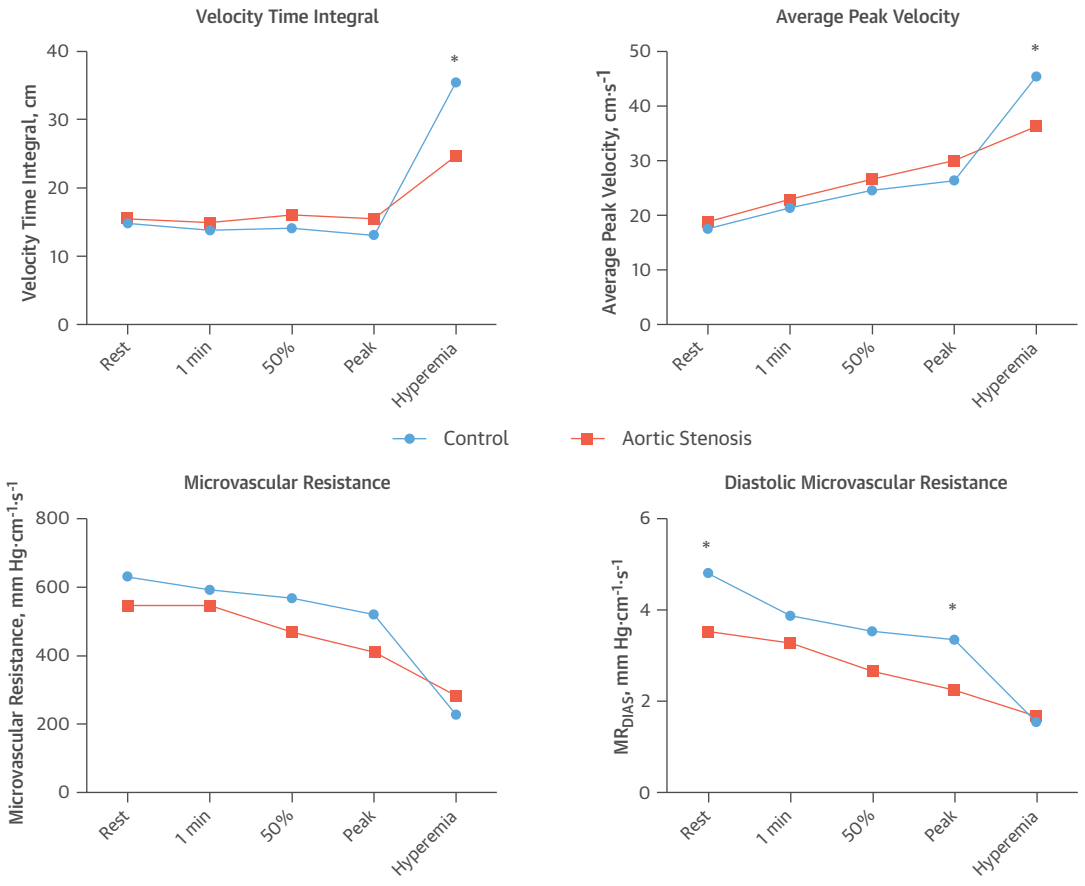
EXTERNAL AND MYOCARDIAL WORK. Controls performed more external work than patients with AS during the catheterization laboratory exercise protocol (98 ± 25 W vs. 77 ± 20 W; $p = 0.005$). The external work in the catheterization laboratory was similar

FIGURE 1 Hemodynamic Response to Stress



Patients with aortic stenosis (AS) and controls had varying hemodynamic responses to supine bicycle exercise and adenosine-induced hyperemia in controls **(blue)** and aortic stenosis **(orange)**. *$p \leq 0.05$. 1 min = after 1 minute of exercise; 50% = 50% of maximal exercise time; bpm = beats per minute; hyperemia = adenosine-induced hyperemia; LV = left ventricular; peak = immediately before exercise was discontinued due to exhaustion; RPP = rate pressure product.

FIGURE 2 Coronary Circulation Response to Stress



Differences between groups were most pronounced with hyperemia. *$p \leq 0.05$. MR_{dias} = diastolic microvascular resistance; other abbreviations as in Figure 1.

to the stress echocardiography protocol experienced in the 13 patients who had both procedures (78 ± 24 W vs. 88 ± 28 W; $p = 0.07$). The cardiac output at rest in the 13 AS patients who underwent stress echocardiography was 5.4 ± 1.6 l/min^{-1} and rose to 9.3 ± 2.5 l/min^{-1} during peak exercise ($p < 0.001$).

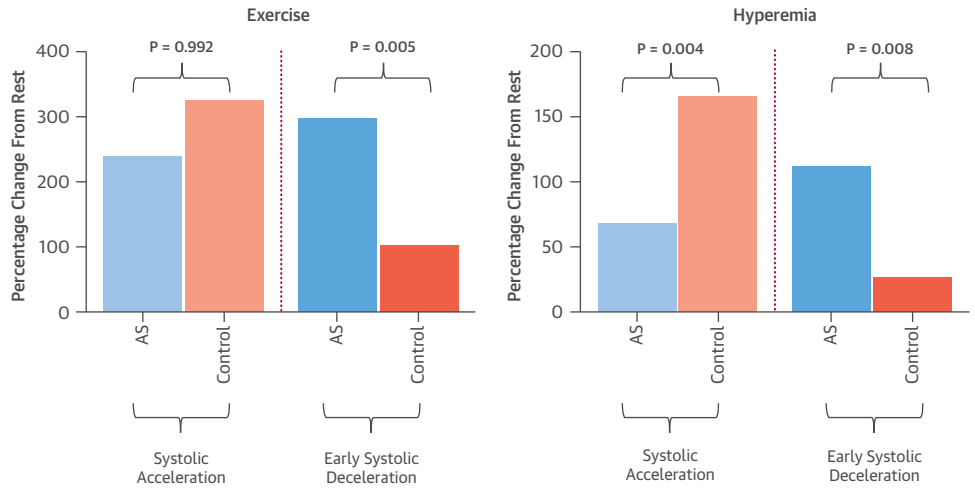
LV pressure was greater in AS compared with controls at rest and at all levels of exercise. Myocardial work, estimated as RPP, was significantly higher for AS patients than controls, at rest (9,707 ± 2,925 mm Hg/min^{-1} vs. 12,721 ± 3,399 mm Hg/min^{-1}, respectively; $p = 0.003$) as well as during peak exercise (20,841 ± 7,622 mm Hg/min^{-1} vs. 27,467 ± 7,260 mm Hg/min^{-1}; $p = 0.02$) (Figure 1).

WAVE INTENSITY ANALYSIS. Typical coronary pressure and flow waveforms, with the corresponding WIA curves, at rest and during hyperemia, in a patient with AS is shown in Online Figure 1. The absolute values and percentage contribution of each of the 4 dominant waves is shown in Online Table 2.

At rest, AS compared with controls had significantly lower early systolic deceleration and lower systolic acceleration with no difference in late systolic deceleration or diastolic acceleration. With exercise compared with rest, for both AS and controls, the magnitude of all 4 waves increased. However, in AS, the increase in the early systolic deceleration was greater than controls (296% vs. 99%; $p = 0.005$) (Figure 3).

With hyperemia compared with rest, all waves increased significantly in both groups, except early systolic deceleration did not change in controls. With hyperemia in AS, the percentage increase in early systolic deceleration was significantly greater (112% vs. 25%; $p = 0.008$) (Figure 3) and percentage change in systolic acceleration

FIGURE 3 Change From Baseline in ESD and SA in AS Patients



During exercise, patients with aortic stenosis (AS) experienced a pathological augmented rise in early systolic deceleration (ESD); during hyperemia, there was a pathological attenuation in the increase of systolic acceleration (SA) and augmentation of ESD.

significantly lower compared with controls (67% vs. 164%; p = 0.004).

These differences in percentage change in early systolic deceleration and systolic acceleration led to a change in the balance of accelerating and decelerating waves from rest to exercise and hyperemia. At rest, accelerating waves accounted for 80% of the forces driving CBF in the AS group and 70% in controls (p = 0.005). On maximal exercise, there was no discernible difference between groups (73% vs. 73%; p = 0.95); with the induction of hyperemia, the resting pattern reversed (70% vs. 78%; p = 0.047) (**Figure 4**).

Resting echocardiographic markers of AS severity, measures of ventricular systolic and diastolic function, and LV mass did not correlate with absolute values of any of the dominant waves at rest, during peak exercise, or in the hyperemic state.

During hyperemia, EOA correlated with the percentage contribution of diastolic acceleration to total WI (r = 0.637; p = 0.006). The same relationship was observed between the percentage contribution of all accelerating waves and EOA (r = 0.603; p = 0.01) (Online Figure 2).

DISCUSSION

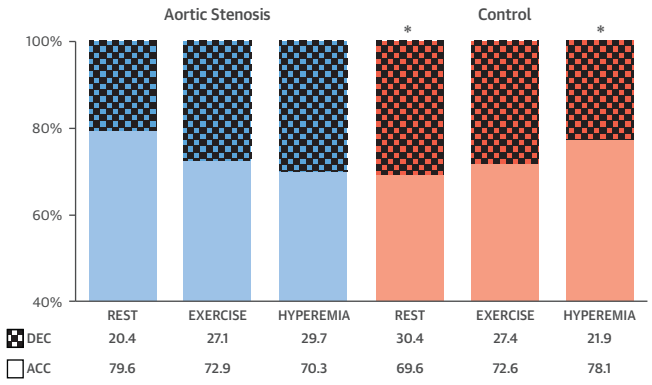
We have shown, for the first time, that it is safe and feasible to carry out supine bicycle exercise during cardiac catheterization in patients with severe AS. This was also the first study to invasively characterize coronary physiological changes in the healthy human heart during exercise.

The main findings of this study:

1. The mechanism of CBF augmentation in exercise and adenosine-induced hyperemia is fundamentally different.
2. Patients with AS failed to alter their CBF in proportion to the increase in cardiac work, making the myocardium vulnerable to ischemia during stress.
3. Minimum MR in AS was not different from controls, supporting the hypothesis that microvascular disease is not a factor in the reduced CFR seen in AS.
4. Diastolic time fraction was lower in AS compared with controls.
5. Although the efficiency of the healthy heart improves during exercise and hyperemia due to an increase in the relative contribution of waves that accelerate flow, the reverse was observed in AS due to an increase in the contribution of waves that decelerate flow.

RESPONSE TO STRESS. In the healthy heart, exercise-induced flow augmentation was characterized by a reduction in coronary MR and a rise in heart rate. Hyperemia led to a greater augmentation in CBF, driven by a more marked reduction in MR but a more modest increase in heart rate than exercise. An important observation is that minimum MR and

FIGURE 4 Percentage of Total Wave Intensity



In control patients, the total percentage of accelerating wave intensity increases in response to exercise and hyperemia (improved coronary perfusion efficiency); in aortic stenosis (AS), the opposite pattern is seen (reduced coronary perfusion efficiency). *p ≤ 0.05 compared with AS. ACC = acceleration; DEC = deceleration.

MR_{dias} were lower with hyperemia than with exercise, signifying that despite exercising patients to exhaustion or limiting symptoms, some microvascular reserve remained.

MR was lower at rest in patients with AS than in healthy controls, particularly the vascular component, MR_{dias}. This helped explain diminished flow reserve (1) in AS patients, where resting microvascular dilation impairs the capacity to further reduce MR in response to stress, a finding consistent with previous studies (16). MR fell to a greater degree with hyperemia than with exercise, but the drop in MR was less in AS than controls. Although MR_{dias} was lower at rest in AS than controls, it was similar in both groups at hyperemia. This indicated a normal minimal vascular resistance in patients with AS, thereby supporting the hypothesis that abnormal cardiac-coronary coupling, rather than fundamental differences in microvascular function, is responsible for reduced CBF in AS. This fit with previous observations that hemodynamic markers of AS severity correlated better with CFR than the degree of LV hypertrophy/mass. Furthermore, several groups have shown CFR to improve immediately after surgical AVR before the regression of LV hypertrophy (6,17,18).

Consistent with other reports (19,20), myocardial work also was greater in AS than controls, pointing to a relative supply/demand imbalance making these patients more vulnerable to myocardial ischemia.

WIA AND CORONARY PERFUSION EFFICIENCY. The relative balance of energy that drives and impedes flow will determine coronary perfusion efficiency. WIA allows quantification of energy fluxes that both accelerate and decelerate coronary flow, providing a measure of perfusion efficiency. The percentage of accelerating wave intensity describes the proportion of energy used in accelerating flow. The greater this value, the greater proportion of coronary energy driving, rather than impeding, coronary flow.

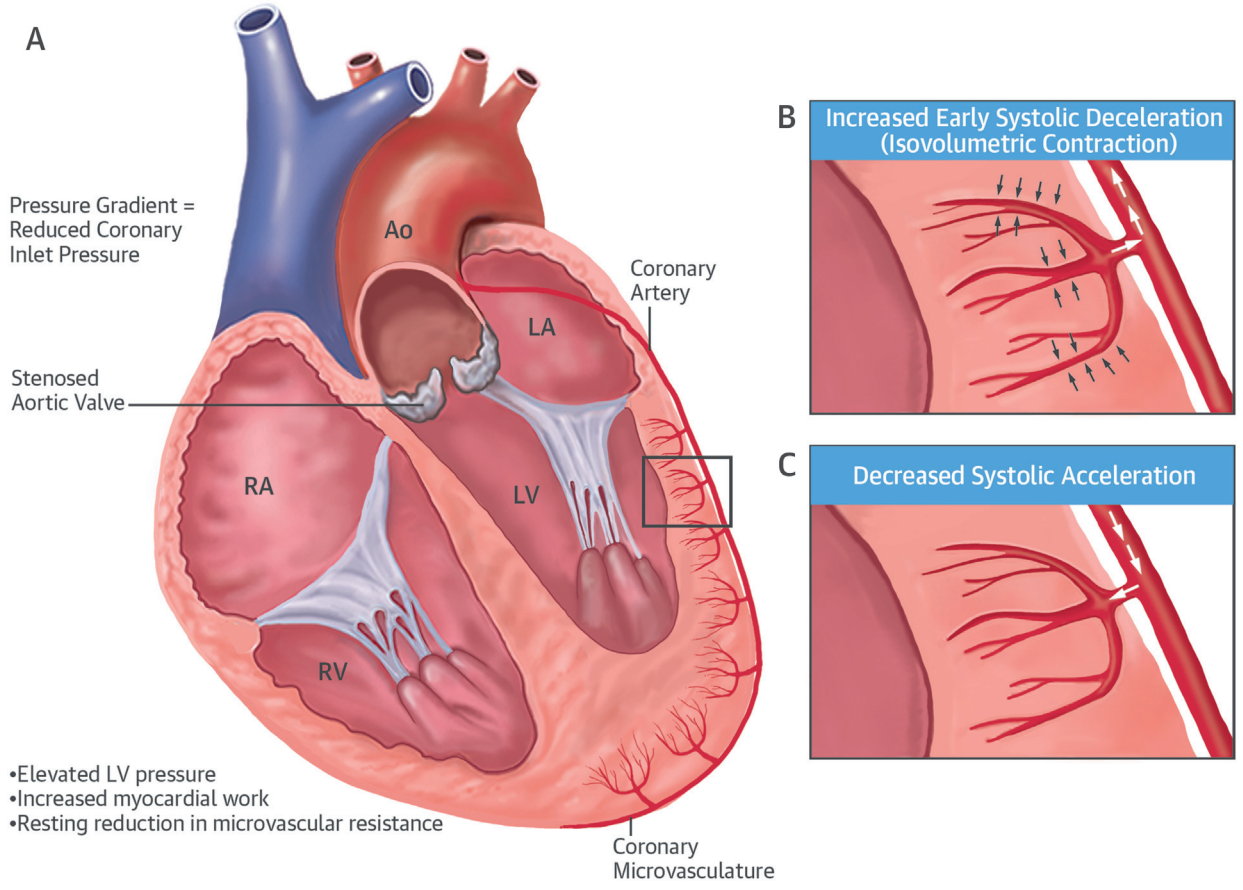
Diastolic acceleration, the principal force driving CBF in the healthy heart, is determined by the degree of ventricular lusitropy. This wave has received the most attention in clinical studies to date (4,5,8). Systolic acceleration originates in the ventricle during ventricular contraction and travels via the aorta into the coronary circulation, thereby accelerating CBF. Early systolic deceleration occurs during isovolumic contraction and is produced from the transmission of rapidly rising LV pressure to the intramural vessels, which decelerates coronary flow.

In healthy hearts, each of the 4 dominant coronary waves increased with exercise, but the percentage increase in the systolic acceleration wave was the greatest. This translated to an increased proportional contribution of accelerating waves to total WI, leading to improved coronary perfusion efficiency. During hyperemia, the magnitude of both accelerating and decelerating waves increased, keeping with findings in animal studies (7,21). As with exercise, the large percentage increase in the systolic acceleration shifted the balance of forces in favor of accelerating waves, improving coronary flow efficiency.

In AS, the increment in systolic acceleration with stress was attenuated compared with controls, particularly during hyperemia, which may relate to the pressure drop across the aortic valve. Furthermore, there was greater exercise-induced augmentation of early systolic deceleration in AS, which likely reflected greater compressive forces in this group during exercise; the larger changes during hyperemia may indicate enhanced cardiac-coronary coupling due to a decrease in vascular resistance. Together, these difference explained the diminished perfusion efficiency during stress in AS.

Although the relative increase in each of the waves was greater with exercise than hyperemia, this increase was more marked with systolic deceleration. Importantly, the augmentation of diastolic acceleration from rest to exercise or hyperemia was not different between AS and controls. Therefore, heightened systolic deceleration and shortened diastolic perfusion time appear to be primary reasons for reduced CFR during exercise and hyperemia in AS.

CENTRAL ILLUSTRATION **Pathological Effects of Aortic Stenosis on the Coronary Circulation**



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In this diagrammatic representation of the pathological environment to coronary flow in aortic stenosis (AS), **(A)** AS causes an elevation in left ventricular (LV) pressure, increasing myocardial work. Furthermore, the pressure gradient across the aortic valve leads to reduction in the pressure at the coronary inlet (reduced driving pressure). Under resting conditions, microvascular resistance is reduced to maintain coronary flow. **(B)** During isovolumetric contraction (aortic valve closed), greatly elevated LV pressure leads to increased compression of the intramyocardial vessels and augmented deceleration of coronary flow. **(C)** Following the opening of the aortic valve, acceleration of coronary flow is attenuated due to a reduced driving pressure secondary to the pressure gradient across the aortic valve. Ao = aorta; LA = left atrium; RA = right atrium; RV = right ventricle.

CLINICAL IMPLICATIONS. With the onset of stress, patients with AS are unable to augment CBF in response to increased myocardial work, creating an environment vulnerable to ischemia that provides a possible mechanism for exercise-induced angina and perioperative cardiac events. This inability to adequately augment CBF is caused by a pathophysiological imbalance of forces accelerating and decelerating CBF in AS and an impingement on diastolic perfusion time (Central Illustration). Furthermore, those with the most severe AS (measured by EOA) are at the highest risk of ischemia.

Although changes in cardiac mechanics are much greater during exercise, hyperemia increases the sensitivity of the coronary circulation to myocardial contraction. Consequently, one might postulate that patients with AS may become particularly vulnerable to ischemia during periods of profound vasodilation and increased myocardial oxygen demand, such as during anesthesia rather than during exercise.

Phasic analysis of coronary flow and pressure by WIA provides unique insight into exercise physiology in AS and has potential diagnostic utility in

identifying asymptomatic patients who should be considered for early intervention, especially if it proves possible to develop a noninvasive method of obtaining these measurements. Exercise WIA may also be useful to assess the effect of therapies designed to increase lusitropy (such as soluble guanylate cyclase activators or phosphodiaesterase inhibitors that increase cyclic guanosine monophosphate) for AS and other conditions that adversely affect cardiac coronary coupling.

STUDY LIMITATIONS. This was a single-center study with relatively small numbers of patients in each group. Patients with AS were older than controls, although we found no correlation between age and absolute values of WI, relative changes in WI, or the total percentage of accelerating or decelerating WI under any of the 3 conditions. Furthermore, we have controlled for differences in baseline parameters by looking at percentage changes with exercise and hyperemia.

We were unable to measure LV pressure simultaneously with coronary physiological data in AS patients and instead, were limited to measuring the former during a separate period of exercise, using an identical exercise protocol. Future studies of this nature would be strengthened by the simultaneous assessment of ventricular dynamics and coronary physiology. Additionally, measurement of myocardial wall stress and, hence, rate stress product may give a more accurate estimate of myocardial oxygen demand.

We did not measure LV mass in all our control cases and thus cannot exclude the possibility that some differences observed may have been related to LV hypertrophy. However, in the AS group, there was no correlation between LV mass and physiological measurements at rest or during exercise.

We calculated wave speed using the single-point method; however, during hyperemia, the wave speed estimated using this method might differ from the true wave speed (22). We measured MR during mid-to-late diastole, when myocardial compressive forces are at their lowest (11), to approximate the vascular component of MR, although this is likely to be an oversimplification as it does not account for microvasculature compliance.

CONCLUSIONS

We resolved the debate regarding the cause of ischemia in AS with normal coronary arteries by showing that AS patients have a higher workload, normal minimum MR, and shorter diastolic perfusion time compared with controls, thereby demonstrating that microvascular disease is not a factor in AS. Moreover, the data suggested that a greater increase in early systolic deceleration (associated with isovolumetric systolic myocardial compression) was responsible for reduced CFR in AS versus controls. These factors restrict coronary flow in the face of higher workloads, hence making the myocardium more vulnerable to ischemia during conditions of stress.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Impaired CFR in patients with severe AS is associated with angina even in the absence of obstructive coronary disease. The efficiency of perfusion, assessed as the balance of energy that drives and impedes flow, increases with exercise in healthy hearts, but decreases in patients with AS because of early systolic deceleration. Ischemia in patients with AS is therefore due to abnormal cardiac-coronary coupling rather than microvascular disease.

TRANSLATIONAL OUTLOOK: The development of noninvasive methods to evaluate phasic coronary flow could have diagnostic value in identifying asymptomatic patients who should be considered for early intervention or assessing therapies that favorably influence cardiac energetics.

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APPENDIX For supplemental figures and tables, please see the online version of this article.