Why Angina in Aortic Stenosis With Normal Coronary Arteriograms?

K. Lance Gould, MD; Blase A. Carabello, MD

Hypertrophy is considered one of the major mechanisms of the myocardium for adapting to hemodynamic overload. More muscle mass provides more contractile elements for generating the extra work required by the overload. In pressure overload of aortic valve stenosis, concentric left ventricular hypertrophy (LVH) normalizes wall stress, a key determinant of ejection performance. Afterload is often expressed as wall stress (pressure-radius/thickness). As the pressure term in the numerator increases, it is offset by an increase in the thickness term of the denominator. In this way, the high systolic pressure required to drive blood through even a very stenotic aortic valve can be consistent with normal afterload and normal ejection fraction.

Unfortunately, hypertrophy not only provides benefits but also has many pathological consequences. One of these is myocardial ischemia and the attendant angina reported by patients with aortic stenosis despite normal epicardial coronary arteries. The onset of angina greatly increases the risk of sudden death compared with the risk in asymptomatic patients with aortic valve stenosis.

Angina occurs when myocardial oxygen demand exceeds supply. Demand is proportional to heart rate and wall stress, and the latter can be elevated in cases of aortic stenosis when hypertrophy is inadequate to normalize stress. After aortic valve replacement, there is marked regression of hypertrophy that may occur over the next several months to years, but angina is relieved immediately. Relief of angina immediately after surgery is probably due to the combination of sudden decreased oxygen demand after removal of pressure overload and increased oxygen supply of improved perfusion.

However, there are remaining questions about the physiological mechanisms for reduced myocardial oxygen supply (coronary blood flow) in aortic stenosis and its improvement after relief of pressure overload. Specifically, what is it about critical aortic stenosis that is "critical" in limiting coronary blood flow causing the first ominous symptom of angina? The answer has been elusive. We know that in humans, coronary flow reserve (CFR) is reduced in aortic stenosis. Although this factor must in some way contribute to the potential for ischemia to develop, there is no difference in the flow reserve of patients with versus those without angina. Thus, reduction in flow reserve alone at normal resting heart rates does not explain the symptom.

Much of our knowledge about coronary blood flow in LVH has come from animal models of ventricular hypertrophy. The models usually differ physiologically from the aortic stenosis found in humans, and of course, there is no way to know whether the model causes angina. Nonetheless, important mechanistic data have been gleaned from animal studies of LVH as follows. First, there is reversal of the normal endocardial-epicardial ratio for coronary blood flow. Normally this ratio is \( \approx 1:2:1 \), appropriate to meet the increased oxygen demands of the endocardium, where wall stress is higher than in the epicardium. It is clear that this ratio is reduced and even reversed in LVH, especially during exercise or pacing.

Second, as noted above, CFR is compromised in LVH. Mechanisms involved include (1) reduced diastolic coronary filling time during the tachycardia of exercise or pacing, (2) increased diastolic filling pressure that compresses the endocardium and inhibits perfusion, and (3) relatively reduced capillary density with fewer capillaries per unit of myocardial volume perfused.

From the foregoing, one would expect that all of the physiological parameters determining oxygen demand and/or coronary blood flow, or some combination of them, might predict when a patient with aortic stenosis would develop ischemia and/or angina. On the demand side, the predictive parameters might be heart rate, peak developed left ventricular (LV) pressure, aortic valve area, or inotropic state. On the supply side, LV filling pressure, diastolic filling time, and wall thickness might be expected to predict the onset of angina. Nonetheless, no factor or set of factors has been used to predict when angina will develop, reflecting the general clinical experience that only approximately half of patients with severe aortic stenosis have angina without close correlation in individuals with the measured variables of oxygen demand and supply. Because we do not know the specific factors responsible for the development of ischemia in aortic stenosis in individuals, it is not surprising that we understand even less about the immediate disappearance of angina that occurs in nearly all patients after aortic valve replacement. The immediate fall in myocardial oxygen demand after relief of valve obstruction must be partly responsible. In addition, there is probably significant immediate regression of hypertrophy during convalescence before the patient becomes fully active. However, sudden death still occurs after aortic valve replacement, although at an obviously much lower inci-
Correlated with changes in diastolic filling time (as flow had returned to baseline). For example, in postoperative patients as a group. LV and no improvement in average flow reserve of the ictus system. CFR is a close linear correlation between CFR and diastolic perfusion time reflecting integrated blood flow supply. One year after surgery, there was a modest (27%) reduction in LV mass index after aortic valve replacement; with more time, greater regression might be expected. Although CFR corrected for rate-pressure product improved after LVH regression, they found no change in blood flow per gram of LV and no improvement in average flow reserve of the postoperative patients as a group.

However, CFR in individuals varied substantially and correlated with changes in diastolic filling time (as flow had done preoperatively) but not to changes in LV mass. These results suggest that the critical parameters for ischemia in aortic stenosis may be the interaction of diastolic perfusion time and mechanical severity of aortic obstruction (valve area). This observation is consistent with animal studies showing that (1) only an 8% regression in LV mass produced a large improvement in flow reserve; (2) with relief of canine supravalvular aortic stenosis yielding reduced LV mass reduction identical to that of the Rajappan et al study, adenosine-induced flow reserve returned completely to normal; and (3) in this same study, although CFR with adenosine infusion was normalized, flow with pacing was not. Filling pressure was not a factor. Thus, in animal studies and in the present study, there was no obvious relationship between hypertrophy magnitude and CFR, whereas on the other hand, diastolic filling time appears to be an important determinant of CFR.

Further support for this notion derives from the work of Ferro et al., who reported a precise close linear relation between diastolic filling time at angina threshold during exercise- or pacing-induced tachycardia and arteriographic severity of coronary artery stenosis (in patients without aortic stenosis). This relation demonstrated that for every stenosis severity level, angina during tachycardia developed at a fixed reproducible diastolic filling time. Or conversely, the diastolic filling time at which angina occurred with tachycardia precisely predicted severity of coronary artery stenosis in that study. Interestingly, heart rate did not correlate with onset of angina during pacing. Taking the study by Ferro et al., the present and former studies by Rajappan et al, and the canine paper noted above, an etiologic pattern is emerging. In a 1997 editorial in Circulation, “Why angina pectoris in aortic stenosis,” K.L.G. hypothesized diastolic filling time as a potentially important cause of reduced CFR and myocardial ischemia in aortic stenosis with normal coronary arteries, a premise now strongly supported by the studies noted above.

Despite these pathophysiological insights, we still have no clinical measurement, no “magic number” or tool, to predict when a patient with aortic stenosis will develop angina. Improved surgical techniques have allowed earlier timing of valve surgery and improved risk-benefit outcomes. If we had more specific measurements to predict the imminent onset of angina/ischemia in aortic stenosis, still-earlier surgery just before symptoms developed would help eliminate the small but definite risk of sudden death before symptom onset.

A responsibility of Circulation reviewers is not only to select the best manuscripts but also to suggest questions, insights, correlations, or further studies that improve the scientific contribution of a first-submission manuscript to the literature. In the spirit of scientific discussion, we would again suggest for further study some potential clinical measurements for predicting ischemia and angina pectoris in aortic stenosis in individuals. We suggest that clinical investigation should try to develop a “critical” diastolic filling period.

Because angina with aortic stenosis almost always occurs with exercise and tachycardia, which affect the diastolic filling period, a close linear correlation would likely be found between the diastolic filling time at anginal threshold and severity of aortic stenosis (valve area). For comparably severe aortic stenosis among different people, angina (or other objective evidence of ischemia) would be expected to occur at the same critically short diastolic filling time during tachycardia in the absence of coronary artery disease. Non-critical aortic stenosis or rapid diastolic filling provides adequate myocardial perfusion at even very short diastolic perfusion times during substantial tachycardia. Therefore, the absence of ischemia with pacing tachycardia to achieve even this critically short diastolic perfusion might suggest that aortic stenosis was not severe enough to warrant valve replacement. The value of this critical diastolic perfusion time causing ischemia would have to be determined by progressive pacing tachycardia in patients with aortic stenosis being considered for surgery.

At echocardiography or cardiac MRI used to assess aortic valve area, diastolic perfusion time and the presence or absence of ischemia could be measured with progressive pacing tachycardia. Valve surgery might be deferred (in the absence of syncope or heart failure) in a given patient when pacing to the critical diastolic perfusion time (determined from a group of other patients with severe aortic stenosis) failed to cause ischemia. This physiological end point would in principle also reflect the complex exacerbating effects of coronary artery disease plus aortic stenosis.

Conclusion
Concentric LVH is clearly associated with abnormal coronary blood flow and with compromised CFR. However, compromised flow reserve by itself does not explain the occurrence of angina. As LVH must indirectly influence filling pressure, perfusion pressure, and myocardial oxygen demand, the magnitude of LVH also does not directly correlate with flow reserve or inducible angina. On the other hand, heart rate and diastolic perfusion time clearly influence the propensity to develop ischemia. Thus, experimentally and clinically, the
essential factors limiting oxygen supply in aortic stenosis appear to be the interaction of diastolic perfusion time and mechanical severity of outlet obstruction. The combination of these factors should be tested as a potential adjunct in helping to time aortic valve replacement.

We hope that this editorial and the physiological insights provided by these reports lead to further physiological clinical studies for predicting myocardial ischemia and angina pectoris in individuals with aortic stenosis as a further guide for timing their aortic valve replacement.

References

Key Words: Editorials I stenosis I angina I myocardium I hypertrophy
Why Angina in Aortic Stenosis With Normal Coronary Arteriograms?
K. Lance Gould and Blase A. Carabello

Circulation. 2003;107:3121-3123
doi: 10.1161/01.CIR.0000074243.02378.80
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/107/25/3121

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/