

ROBERT OGDEN BONOW, MD: a conversation with the editor on valvular heart disease and indications for operative intervention

Bob Bonow (*Figure*) was born in Camden, New Jersey, on March 11, 1947, and grew up in the suburbs of New York City. He graduated magna cum laude from Lehigh University in chemical engineering in 1969 and from the University of Pennsylvania School of Medicine in 1973. His medical internship and residency were at the Hospital of the University of Pennsylvania. From 1976 until 1992, Dr. Bonow was in the Cardiology Branch of the National Heart, Lung, and Blood Institute in Bethesda, Maryland. In 1992 he moved to Chicago to be the Goldberg Distinguished Professor of Cardiology and chief of the Division of Cardiology in the Department of Medicine of the Northwestern University Feinberg School of Medicine. He recently was president of the American Heart Association.

Dr. Bonow is one of the world's outstanding cardiologists. He is a superb clinician, a splendid clinical investigator, and a marvelous teacher. He is the author of numerous articles in peer-reviewed publications and recently became one of the 4 editors of Braunwald's *Heart Disease* textbook. He was the chair of the first and second American College of Cardiology (ACC)/American Heart Association (AHA) committees for writing guidelines for management of patients with valvular heart disease. Dr. Bonow gave medical ground rounds at Baylor University Medical Center (BUMC) on September 14, 2004, and discussed indications for operative therapy in patients with aortic stenosis, aortic regurgitation, and mitral regurgitation. Thereafter, Bob and I had a discussion on valvular heart disease.

William Clifford Roberts, MD (hereafter, WCR): *Bob, I appreciate your willingness to talk to me and therefore to the readers of BUMC Proceedings. To start, could you discuss valvular heart disease in general, the magnitude of the problem, and your general guidelines for recommending a cardiac valve operation?*

Robert Ogden Bonow, MD (hereafter, ROB): Bill, first it's an honor for me to visit BUMC, to give grand rounds, and to spend time with you. We are seeing more and more patients with valvular heart disease because of our aging population. General internists and even cardiovascular specialists are a bit uncertain about the most appropriate evaluation and treatment for patients with valvular heart disease. Unlike coronary heart disease and heart failure, where results of many trials allow specific guidelines for management, there are no prospective randomized trials with definitive results for patients with valvular heart disease, and therefore the guidelines are based only upon consensus of experts. As cardiovascular specialists we expect evidence to guide our decisions, but the evidence in patients with valvular heart disease



Figure. Dr. Robert Bonow during the interview.

is primarily retrospective from individual medical centers and based on relatively small numbers of patients. Unfortunately, there are wide differences in opinion among experts in management of these patients. As a consequence, the threshold for proceeding with a valve operation may vary tremendously from place to place depending upon the expected results of the surgeons as well as the skill of the referring cardiologists.

WCR: *You were the chair for development of the latest ACC/AHA guidelines for operative intervention in valvular heart disease. How did that endeavor come about, how was the committee formed, and who made up that committee?*

ROB: It came about in the mid 1990s when the ACC/AHA guidelines task force began moving from procedure-driven guidelines to disease-based guidelines. In the future we'll be seeing fewer procedure-related guidelines and more patient management guidelines. We realized from the beginning that formulating guidelines for valvular heart disease would be a challenge because of the lack of data from randomized clinical trials. The committee was composed initially of 10 to 12 physicians appointed by the chair of the guidelines task force, which also appointed the chair of the writing group. The committee consisted of very knowledgeable and influential physicians who had written extensively on valvular heart disease. The committee included one pediatric cardiologist (Michael Freed), one family practitioner (Brad Fedderly), and one cardiac surgeon (Hank Edmonds); the remainder of the members were adult cardiologists, including both echocardiographers and interventionalists. The committee consisted of a good balance of physicians.

WCR: *How many meetings did you have?*

ROB: Initially, the plan was for the committee to meet a few times and complete the written document in 18 months. We realized early on, however, that that timetable was unrealistic.

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We found ourselves arguing, for example, for 3 hours on the definition of *severe* aortic valve stenosis. Should the definition be based on valve area, the transvalvular gradient, or the echo Doppler velocity across the valve? That definition was important because several committee members believed that valve replacement should not be recommended unless the degree of stenosis was severe. Was severe aortic stenosis a valve area of 1.0 or 0.8 cm²? Ultimately, we decided it didn't matter too much because the real indication for operation for aortic stenosis was not how tight the valve was but what effect the obstruction had on the left ventricle and on the patient. An asymptomatic patient with normal left ventricular function was not a candidate for aortic valve replacement irrespective of the severity of the obstruction. Once the symptom status of the patient and the presence or absence of normal left ventricular function were settled, we returned to the question of the severity of the obstruction.

The committee members could discuss a single item for hours. The discussions took several meetings, usually in Chicago (a central location), and they generally lasted 1½ days. We then assigned a specific topic to each committee member. As the manuscripts were submitted, they were circulated to other committee members for comments. Thus, thereafter we had drafts to discuss at the meetings. Not everybody got their drafts in on the specified date, but that individual lateness proved helpful because it allowed focus on the individual components rather than on the whole document. The process took about 2½ years to complete. We're now revising the guidelines, which were formulated in 1998. The revision has been in progress for about 1½ years, and we're hoping to complete this revision in the fall of 2004 and have it published in the spring of 2005.

WCR: *In the 1998 guidelines, which section of the initial draft did you prepare?*

ROB: The one on aortic regurgitation. The committee actually voted on who wrote which portion initially. Every section, however, had input from all committee members. Every line, every nuance, was carefully reviewed. The 1998 guidelines were the lengthiest ones in any area up to that time. The document consisted of 102 pages in the *Journal of the American College of Cardiology*, including over 730 references! I'm not suggesting that length represents excellence. Guidelines ideally contain concise bullet points such that physicians can put them in their pocket or Palm Pilot and memorize them for patient management. Our guidelines in 1998 were based on consensus, not on large-scale clinical trials, and, therefore, we believed it important to discuss, sometimes at length, why a certain recommendation was being made. We included lots of information about natural history, pathophysiology, and whatever clinical evidence was available. Although we created a very lengthy document, we also had an executive summary that distilled the huge amount of information into a pocket guide. In essence, we wrote a textbook on valvular heart disease.

WCR: *As chair of the committee, you went over every word multiple times?*

ROB: Yes, I did. Since each section was prepared by a different committee member, the document had many different styles. I tried to make it more cohesive, and that took much editing and rewriting. That created lots of e-mails and conference calls. Each

committee member had a chance to go over every word. I read it several times.

WCR: *Who paid the expenses of the committee: flights, hotels, secretarial assistance, etc.?*

ROB: The expenses were covered by a budget created jointly by the AHA and ACC. Both organizations had decided in the 1980s to focus on quality—not only for their members but also for the American public, for managed care, and for everyone involved in the medical enterprise. Both organizations have invested substantially in a very rigorous guidelines process. In fact, the process itself was well articulated in a 2-part review article in *Circulation* in 2003 by Ray Gibbons, the outgoing chair; Elliott Antman, the current chair; and Sid Smith, the incoming chair of the ACC/AHA task force.

WCR: *When you went to the National Heart, Lung, and Blood Institute in 1976, cardiac valve replacement was the number one operation being done there. The studies you did on aortic regurgitation there were the first attempt to put science into the process of managing patients with valvular heart disease.*

ROB: I think that's a fair assessment, Bill. I arrived at the National Institutes of Health (NIH) when the foundations for this effort were already in place. Your laboratory was studying valve diseases extensively and had written lots on the topic. Stephen Epstein, Walt Henry, and Jeff Borer had created some prospective protocols to enlist patients with aortic valve disease and mitral valve disease. I cannot take credit for devising these protocols. Although some protocols were already in place, others were not. Two major groups of patients were studied. One group consisted of patients who had already had valve replacement, and we examined preoperative characteristics that would predict outcome. To define the natural history, the second group consisted of patients who had not had valve operations. At that time, echocardiography was brand new. This new technique could not only evaluate the valve but could also determine left ventricular dimensions and function.

At that time, little was known about predicting outcomes in patients with valve disease. In the 1970s, we waited for patients to have symptoms before recommending valve operations because the results of valve replacement were not as fully developed as they are currently. Outcome after valve replacement depended on the type of substitute valve inserted, on the operative skill and technique of the surgeon, and on the functional status of the patient preoperatively. We learned that if we always waited for symptoms to develop, the outcome was not ideal. Indeed, some patients were not improved by technically "successful" valve replacement. It became apparent that waiting for symptoms as the only indication for surgery, at least in some patients, was waiting too long. Echocardiography not only allowed preoperative evaluation but also served as an excellent tool to follow patients postoperatively.

The first study that Walt Henry and I did (Walt was the first author of the first couple of papers) demonstrated that echocardiography in both aortic stenosis and aortic regurgitation could identify a group of symptomatic patients undergoing surgery in whom the postoperative outcome was poor. The patients with increased mortality after valve replacement were those who preoperatively had left ventricular systolic dysfunction (that is, impaired pump function), such as a low ejection fraction, and

increased end-systolic and end-diastolic left ventricular dimensions. Although the findings were true of both aortic stenosis and aortic regurgitation, they were more predictive in the latter group than in the former group. We found a very high risk subset in the aortic regurgitation group. We were the first to publish the predictive value of either ejection fraction or fractional shortening, which we measured by the echocardiogram.

Others confirmed our findings. Not all other investigators confirmed the same threshold values that we found or the particular numbers that we found predictive for ejection fraction or end-systolic left ventricular dimension, but those 2 parameters have stood the test of time. One reason others found different thresholds was that they studied less sick patients. Cardiologists now tend to refer patients earlier for valve replacement or repair. Presently, we recommend valve operation when the ejection fraction begins to fall or the left ventricular end-systolic dimension begins to increase. As a consequence, the results of the valvular operations now are better than in earlier years.

WCR: *You're talking about pure aortic regurgitation?*

ROB: Right. That was an important series of studies. The other series of studies also was quite important. That involved an examination of the natural history of the disease and the predictors of symptoms. These turned out to be the same variables, namely left ventricular systolic dysfunction as determined by left ventricular ejection fraction and left ventricular end-systolic dimensions. The patients with the larger left ventricles and the lower ejection fractions were the ones who developed symptoms, particularly when those 2 factors worsened over time. When we started operating sooner in patients with aortic regurgitation because of evidence of left ventricular systolic dysfunction by echocardiogram, the patients had better outcomes postoperatively. The duration of the left ventricular systolic dysfunction also was an important predictor of outcome after valve replacement.

WCR: *Your patients were asymptomatic when you initially studied them?*

ROB: That's right. Some developed symptoms with time and then they were included in the surgical group.

WCR: *The ejection fractions in those early studies were determined by echocardiogram?*

ROB: They were determined initially by left ventricular angiography and then, as echocardiography became available, by this latter method. The protocols that we developed were really pristine. (One reason the intramural programs at NIH need to be preserved is because the protocols created there can be very tight and rigorous.) For example, all of our preoperative patients had an echocardiogram, an electrocardiogram, and a cardiac catheterization with angiography. Six months after valve replacement, the patients returned, and all of those studies were repeated. Then, after that, they would have an echocardiogram every year. When other techniques came along in the later 1970s, such as radionuclide angiography, then every patient had that study as well. Initially the ejection fractions in the preoperative patients were predominantly determined by echocardiogram because this was the method by which patients were followed postoperatively. By the 1980s, however, radionuclide angiograms became the gold standard for ejection fraction.

WCR: *The cut-offs for normal vs abnormal left ventricular ejection fraction by either echocardiogram or angiogram seem to vary*

considerably. I have observed that one reader would estimate the ejection fraction to be 65%, another 50%, and another 40%. If you use 60% as the cut-off for proceeding to valve operation, these interpretations must be accurate. The variation in estimating ejection fraction worries me a good bit.

ROB: It worries me too. We all see patients who have a 55% ejection fraction but may have had this level of left ventricular function for the last 10 years. In patients like that, I would not recommend valve surgery, but I would recommend valve operation if the ejection fraction had been 75% earlier. I agree that many times the ejection fraction is under- or overestimated. I saw a patient recently with aortic regurgitation who had good left ventricular systolic function by serial echocardiograms over the last 6 years, and the end-diastolic dimension measured by different people ranged from 58 to 68 mm with no particular trend and considerable scatter within this range. I explained to the patient that the left ventricle is shaped like a strawberry and that the measurements obtained depend upon whether the measurement was along a true short axis or not. These measurements do vary depending on location of the measurement, not to mention the physiologic variations in ventricular size depending upon blood pressure, amount of regurgitation, and heart rate. There's much variability in the measurement and also in the physiology.

The message here is that an important decision, like whether to perform a valve operation, should not be based upon a single measurement. There's always time to repeat the measurement or obtain the ejection fraction by a different technique such as radionuclide angiography, which can be quite precise. Magnetic resonance imaging (MRI) will probably be used more in the future because it can determine chamber volumes, ejection fractions, and dimensions very accurately. I've been recommending more studies of MRI to all physicians involved in imaging research in valve disease. When the left ventricle enlarges, it doesn't always do so in the same way. In some patients it elongates; in others it becomes more spherical. MRI can do a much better job of sizing up ventricular volume and function than either 2-dimensional echocardiography or angiography. Three-dimensional echocardiography also will provide more precise measurements than either 2-dimensional echocardiography or angiography.

We have a series of protocols now in our lab using both 3-dimensional echocardiography and MRI in patients with valve disease, trying to replicate what we did in the 1970s. Such protocols are much more difficult to perform now. In the 1970s, we simply followed patients until symptoms occurred. It was a straightforward decision-making process. Now in a large, complex medical center with >50 cardiologists managing their patients, each one has a different threshold for proceeding. We can't control when and how each cardiologist sends his or her valve patient to operation. We can look at patients who are going to surgery, evaluate their left ventricular function, and examine the result of the operative procedure, but it is more difficult now to have a homogenous group of patients or to define natural history.

WCR: *Your discussion here of aortic regurgitation concerns only patients with chronic and not acute aortic regurgitation?*

ROB: Correct. Our guidelines, however, also consider acute aortic regurgitation, and the criteria for valve replacement in that circumstance are different.

WCR: You mentioned in your presentation earlier today that aortic regurgitation, in contrast to aortic stenosis, has a number of different etiologies. Sometimes it's due to an abnormality of the valve, sometimes to an abnormality entirely of the ascending aorta, and, on occasion, to both. Are your criteria for operation the same regardless of etiology?

ROB: That's a very important point because today we see more and more patients whose aortic regurgitation is due entirely to disease of the aorta. For example, high blood pressure can lead to aortic regurgitation. Patients with congenitally bicuspid aortic valves also often have dilated ascending aortas due to medial deficiencies. In many patients, the valve condition alone causes regurgitation, but associated aortic root enlargement makes the valve malfunction more severe. Whether the aortic regurgitation is due to valve disease or to disease of the aorta or to both does not change the effect of aortic regurgitation on the left ventricle and therefore the need or the lack thereof for valve replacement.

In some cases, though, the principal concern is the disease of the aorta, and the ascending aorta needs to be replaced or repaired because it is enlarging too much even though the degree of aortic regurgitation is relatively mild. The criteria for operative intervention on the aorta is a dimension of 50 to 55 mm in diameter measured just above the sinotubular junction. There are other issues in these patients. Should they exercise? Should they be on beta-blockers? We have no information. Proper recommendations regarding pregnancy, which may further enlarge the aortic root, are also difficult to formulate because of lack of a strong evidence base.

WCR: Replacing a portion of ascending aorta makes for a much more complex operation than replacing only the aortic valve. The frequency of replacing both has clearly increased in recent years both in patients with pure aortic regurgitation and in patients with aortic valve stenosis. Whether 50 or 55 mm is the proper criterion for aortic replacement in these patients is unclear to me. To use these same numbers for a 100-pound woman and a 220-pound man seems inappropriate. I think the move to excise and replace a portion of ascending aorta has gone too far in recent years. What is your view?

ROB: I agree that we don't really know what the right threshold is, and body size or body mass index has not been evaluated thoroughly in this area. I think either subconsciously or by correction of these measurements to body surface area, we make these assessments when we're managing individual patients. Certainly, a small woman normally has different ventricular and aortic sizes than a huge man.

WCR: Do you think that body surface area ought to be replaced by body mass index?

ROB: I don't know, but probably. Body surface area has never for me been a very good correction factor. I haven't used it. Body mass index may be better, but we don't have data yet on it.

WCR: Could you summarize then the indications for aortic valve operation with or without simultaneous replacement of the ascending aorta in patients with pure aortic regurgitation?

ROB: The guidelines provide a very complex table of class I, IIA, and IIB indications. There are 4 or 5 bullet-point take-home messages. Symptoms are the most important indication for valve surgery. One of the most important tests we do is to take a careful history. It's complex because many patients with aortic regurgitation have mild symptoms that do not warrant surgery.

It's rare to find a patient with significant aortic regurgitation who is unequivocally asymptomatic, as many note fatigue or mild dyspnea. Sometimes an exercise stress test is helpful in eliciting unrecognized symptoms in a sedentary individual. Without symptoms I would recommend surgery if the ejection fraction is <50%, if the left ventricular end-systolic dimension is >55 mm, or if the end-diastolic dimension is >75 mm. Body size must be kept in mind for all of these dimensions. The 75-mm diastolic dimension was based upon data in which 80 mm preoperatively led to poor results. But in the current era, we rarely see dimensions close to those figures as we tend to operate before the left ventricle dilates to this degree.

When using these numbers, we run the risk of waiting too long in patients, even though I'm concerned that we may be operating too early in others. In patients who are being followed carefully with good measurements—and those numbers progressively increase or the ejection fraction progressively decreases, or both—these fixed numbers do not have to be reached if the patient is getting close to these thresholds and the surgical expertise in that hospital setting is superb. Guidelines are created as helpful recommendations to improve quality. Every physician, however, has to make decisions that are sometimes quite difficult. Do guidelines set the highest bar or the lowest bar or in between? Are we trying to set the standard which we know everybody can achieve and therefore everybody would accept? Or, are we trying to set the goal at a higher level of quality? Wouldn't it be good if we could all achieve that higher level? But, then you're running the risk that not every center can achieve these results.

Getting back to aortic regurgitation, the final bullet point is related to the aortic root. Is the aortic root enlarged or enlarging? The current recommendation is a threshold of a 50-mm diameter, realizing that it's a consensus. There are few good data. Some physicians would use a higher or lower threshold. The whole issue of body size must be considered.

WCR: Let's discuss aortic stenosis. It obviously is more common than pure aortic regurgitation. At the NIH, patients with valve disease were divided into 2 categories: those with "predominant regurgitation" and those with "predominant stenosis." I've never liked that arbitrary classification because "predominant regurgitation" means that there is some stenosis and thus the valve cusps are unequivocally structurally abnormal, whereas in pure regurgitation the valve structure may be entirely normal. If a patient has wide-open aortic regurgitation but a peak systolic transvalvular gradient of 20 mm Hg, how do you classify that patient?

ROB: That sounds like pure aortic regurgitation because if the regurgitation is severe you might anticipate some degree of outflow pressure gradient because of the enormous forward stroke volume against what may be a structurally normal valve. Then again, a small transvalvular gradient may reflect some stenosis although the lesion appears to be mostly aortic regurgitation.

WCR: I have never seen a structurally normal valve in a patient whose transvalvular peak systolic pressure gradient is >10 mm Hg.

ROB: During exercise, huge stroke volumes may cross the aortic valves, and a 10- to 20-mm Hg transvalvular gradient may be the consequence. Usually these large volumes in themselves do not produce a precordial systolic murmur. Patients with pure aortic regurgitation, however, always have a systolic murmur, presumably because of the huge stroke volume going across the

valve during ventricular systole. In fact, the systolic murmur is often easier to hear than the diastolic murmur.

WCR: *You include patients in your studies with “pure aortic regurgitation” if the peak transvalvular systolic gradient is ≤ 30 mm Hg?*

ROB: Yes, it was ≤ 30 mm Hg. Thus, we did include patients who had mild aortic stenosis. Many patients, of course, have both aortic regurgitation and stenosis. The guidelines we just discussed for patients with aortic regurgitation do not necessarily apply to patients with both regurgitation and stenosis. Guidelines for patients with both mitral and aortic valve disease are even more difficult to develop, although we attempted to do so.

WCR: *What are your criteria for operation in adults with aortic stenosis?*

ROB: The guidelines also have a section for adolescents. We did not deal with a preadolescent pediatric population.

WCR: *Essentially, your guidelines concern patients >10 years of age?*

ROB: Yes. The very young are quite different, and they tend to be seen by a different group of physicians. The best methods to assess the severity of aortic stenosis have varied. In those ≤ 10 years of age, the peak transvalvular pressure gradient is the most commonly used measurement, whereas in adults it is the mean transvalvular gradient or the valve area. The pediatric cardiologists have defined the natural history of aortic stenosis using the peak-to-peak gradient, but that measurement is not really physiologic since those peaks occur at separate times during ejection.

What gradient to use in evaluating the severity of aortic stenosis in adolescent patients with congenital aortic stenosis created much discussion in the guidelines committee. We distributed our recommendation widely through the American pediatric cardiologic community. Although only one pediatric cardiologist was on the committee, we had a lot of input. In addition to weighing the pieces of evidence and going over them word for word, the committee sent the guidelines to a number of outside consultants. Unlike an original manuscript submitted for publication, in which you get 2 or 3 reviews that authors respond to, it's not uncommon in guidelines development to have 50 or 60 reviewers with extensive comments. Sometimes the reviewers were chosen because they were experts in a specific area. Although they might have been asked to read the entire document, we really wanted their comments only on a specific area. Although we had only 1 surgeon on the committee, we had input from a number of well-known cardiac surgeons, and they often disagreed with our recommendations and even with each other, and we had to address those differences. Then we revised the guidelines appropriately.

WCR: *To develop the first guidelines, you and your colleagues spent 2½ years, with numerous e-mails, a lot of your secretarial time to type what you had dictated or written, and huge amounts of editing time. You were responsible for the whole thing and you made it read like it came from a single author. Were you paid anything for your efforts?*

ROB: No, I wasn't paid. All committee members were volunteers. Furthermore, the president of the American Heart Association and its other officers were not paid.

WCR: *I think it's important for lawyers and others who use these guidelines to know that they were prepared free of charge by physicians*

using their professional time, their family time, their university time, or whatever to do them.

ROB: That's true.

WCR: *Now back to aortic stenosis. The aortic valves are like fingerprints. No two are alike. Let me return to the problem of the best way to determine the severity of the stenosis. You mentioned the peak-to-peak transvalvular gradient, the mean gradient, and the valve area. You also mentioned in your presentation that patients with so-called “low cardiac output—low gradients” nevertheless can have severe aortic stenosis. With peak transvalvular gradient, you've got a single measurement, whereas with valve area there are several variables including heart rate, ejection fraction, a constant, etc. Dallas is a valve-area town. I've seen operatively excised aortic valves in patients not having simultaneous coronary bypass with small valve areas (<0.8 cm²) but peak gradients of <20 mm Hg. It appears that the valve area may be less accurate when the peak gradient is small. I'm referring to patients with normal cardiac outputs and ejection fractions. Your comments?*

ROB: Those are excellent points. The complexity of evaluating individual patients makes writing guidelines difficult. All these factors need to be considered. If we accept the view that the valve area is really what is going on physiologically—assuming it is measured accurately—then recommendations can start there. That makes a lot of sense. But, how you get there is something else. If things do not fit together properly for an individual patient, I would try to look at the big picture as best I could. If the valve area was 0.9 cm², the cardiac output was normal, and the peak gradient was only 16 mm Hg, then these variables do not fit together very well. I either need more information or I'm going to ignore one of those variables. If the patient is asymptomatic with normal left ventricular function, that patient doesn't need surgery regardless of the valve area. If the patient has symptoms, then it's something else because then you want to know whether the symptoms are caused by the aortic stenosis or whether valve replacement would not only improve the symptoms but also prolong life. Then, I think you do need more information to get a feeling for how tight that valve really is.

WCR: *With aortic stenosis, if the patient is asymptomatic you don't operate except under very unusual circumstances. What about the 50-year-old man who runs 15 to 20 miles a week (he has a loud ejection murmur typical of aortic stenosis), and by echocardiogram, lo and behold, the calculated peak transvalvular gradient is >110 mm Hg. Is anybody really asymptomatic with that degree of obstruction?*

ROB: Well, these are also good points. You and I just made the statement that you wouldn't operate upon asymptomatic individuals except in very unusual circumstances. Sometimes unusual circumstances are kind of usual. The natural history studies often do not include patients with peak transvalvular gradients >100 mm Hg. In the Mayo Clinic series, for example, nobody with aortic stenosis died without first developing symptoms. They excluded a number of patients, however, who went directly to surgery. The patients who went directly to surgery were those patients with very high transvalvular gradients. This raises the possibility that the outcomes were good in that asymptomatic group because the clinicians had made the correct decision to operate on the ones with the most severe stenosis. The overall mortality of asymptomatic patients with aortic stenosis (defined as a valve area <1.0 cm²) is $<1\%$ per year! This has to be bal-

anced against the operative mortality rate of >1% for aortic valve replacement in this country.

However, I too am concerned about an individual patient who has very severe stenosis. Perhaps exercise tests in the young or middle-aged athletic man might be useful. Some patients who claim to be asymptomatic will for the first time develop symptoms during exercise stress testing. That was shown by Dawson and coworkers. Twenty-five percent of their patients developed symptoms “for the first time” on a treadmill. They were either denying symptoms or just weren’t pushing themselves during normal activities. You can also observe the blood pressure response to exercise treadmill testing, and other variables can be assessed during echocardiographic stress testing. We do recommend that valve replacement is reasonable if the blood pressure fails to increase or actually decreases with exercise. I’ll admit that I’ve got some patients with a valve so tight that I’m very nervous. If the person is very vigorous and athletic I might recommend valve replacement earlier.

We actually do make recommendations in the guidelines, totally based on consensus, as to what degree of aortic stenosis by itself would be enough to recommend aortic valve replacement. We couldn’t decide on anything higher than a valve area of 0.6 cm², which is a very stenotic valve. We also considered other measurements of stenotic severity, such as the peak aortic valve gradient, the mean gradient, or the peak left ventricular systolic pressure. There was enough consensus that severe aortic stenosis in and of itself would be an indication for valve replacement, but we did not come up with rigid guidelines that everyone would agree upon other than a valve area of ≤ 0.6 cm². Other than that, it’s a decision we have to make in individual patients. We did agree that if the degree of obstruction is severe enough to cause left ventricular systolic dysfunction (an ejection fraction <50%), surgery should be performed.

WCR: *In your presentation, you mentioned the article by Ross and Braunwald in 1968 on the natural history of aortic stenosis. That article of course has been hugely quoted. As I recall, the number of patients in their study was only 15 or 16, a very small number, but each of them had had cardiac catheterization, so they knew the severity of the stenosis. That was the unique feature. But surely you wouldn’t base the natural history of many diseases on only 15 patients!*

ROB: Yes, we all have had that figure implanted in our mind, and most of us have a slide from their article. Other studies, however, have confirmed their findings. Kelly and coworkers at the University of Virginia reported another natural history study that demonstrated that in asymptomatic patients with aortic stenosis the outcome is good, in that patients don’t die before they develop symptoms. They had 2 deaths among their patients, and both patients developed symptoms first. (There are a few patients who fell through the cracks who retrospectively did develop symptoms before they died, but they died before surgery could be performed. That’s why patients with aortic stenosis must be followed very carefully when they have severe aortic stenosis.) But to address your point, Kelly et al also reported a second group of symptomatic patients with severe aortic stenosis who did not undergo surgery (for whatever reason). The mortality rate in them over the course of 2 to 3 years was 50%! They replicated the Ross and Braunwald diagram 20 years later.

WCR: *You mentioned that once a person with aortic stenosis develops symptoms it is time to operate. Is the prognosis similar or different with the 3 symptoms—dyspnea, chest pain, and syncope?*

ROB: It’s difficult to know for certain. The Ross and Braunwald schematic has different slopes for each of the 3 different symptoms: heart failure has a deeper slope than angina pectoris, which has a deeper slope than presyncope. I tend to treat them as equal culprits. With any symptom I recommend surgery. Now having said that, what do you do with a patient who’s only mildly dyspneic? It’s much trickier because it’s not overt heart failure, which was what Ross and Braunwald were talking about: 50% mortality in 2 years if you had severe heart failure. The patients of Ross and Braunwald had severe heart failure. Is the mild dyspnea the result of aortic stenosis or the consequence of growing older and becoming more out of shape? The mild dyspnea might not even be recognized by the patient; the patient may attribute it to being out of shape and may not report it to the physician. We all have patients like that. It’s a clinical judgment of how much dyspnea is enough to convince you that it’s coming from the heart and therefore is significant enough to warrant valve replacement. A stress test in this circumstance might be helpful, although everybody gets dyspneic on a treadmill sooner or later.

WCR: *You tell a patient with aortic stenosis that his or her aortic valve has some degree of obstruction, and, although there are no symptoms now, once symptoms develop, aortic valve replacement will be recommended. After hearing that message, that individual is going to attribute any symptoms that he or she develops in the next 2 years to the valve stenosis irrespective of the degree of the transvalvular gradient.*

ROB: That’s a real issue in practice, but it works the opposite way too. If the patient does not want surgery, he or she may not inform the physician when symptoms develop. This is where everything else has to come into play too. Mild symptoms are more eminent when they develop in a patient with a valve area of 0.7 cm² compared with one with an area of 1.2 cm². First and foremost, we need time to talk to patients. Unfortunately, in the current era we are spread thin and often are not able to spend much time talking with our patients. A good physician with sufficient time can often talk through these things and figure out what’s going on.

WCR: *At the NIH, Dr. Eugene Braunwald advised his colleagues in the cardiac catheterization laboratory to try for up to 45 minutes to get the catheter across a stenotic aortic valve. When the echocardiogram came along, many quit trying to get the catheter across the stenotic valve and settled for coronary angiography alone. How many patients with aortic stenosis do you actually send to cardiac catheterization now to determine the severity of the obstruction as well as the status of the coronary arteries?*

ROB: In the current era, echo Doppler is what we use. A hemodynamic study is not needed to characterize the valve in most patients. Cardiac catheterization is useful when the echocardiographic data are discrepant or imprecise in some way. The problem with the catheterization data is that the valve area calculations are critically dependent on the flow measurements. I’m not sure we always get accurate cardiac output measurements. In a busy cath lab, no one spends 45 minutes anymore trying to cross a stenotic valve. The main reason to perform cardiac catheterization in a patient with aortic stenosis is to determine the status of the coronary arteries.

WCR: *If your patient has good left ventricular function, you will try to get across the aortic valve at the time of cardiac catheterization?*

ROB: Certainly.

WCR: *Could you summarize your indications for doing aortic valve replacement in patients with aortic stenosis (unassociated with mitral valve disease)?*

ROB: Symptoms are the most important determinant. Second, in an asymptomatic person or a minimally symptomatic person, valve replacement is recommended if there is evidence of a declining ejection fraction.

WCR: *If you do 2 studies to get the left ventricular ejection fraction what is the usual difference between them?*

ROB: It depends on the technique. With echocardiography, you get about 8% variability. Thus, 50% and 58% are essentially the same. With radionuclide angiography, the variability is about 5%. Thus, 50% and 55% are the same. With contrast left ventriculography, the variability is greater.

WCR: *Eight percent could make a huge difference in your decision making.*

ROB: Absolutely. If a person really has no symptoms and the decision for or against operation is based on the ejection fraction measurement, you want to be sure that it really is low. If there is any question, you can repeat it or verify it by a different technique. That's why I say "below normal." If it goes from 55% to 50%, that could be physiologic variation only. It's also rare for a patient with aortic stenosis to have true left ventricular systolic dysfunction and be asymptomatic. If that circumstance occurs, I would worry about associated coronary heart disease for its cause.

That brings up a third indication for surgery for aortic stenosis: the patient with severe stenosis who is undergoing coronary bypass surgery. What severity of aortic stenosis warrants aortic valve replacement in the patient whose symptoms appear to be the consequence of coronary artery disease and who is to have coronary bypass surgery? The decision is easy if the aortic stenosis is severe: the valve should be replaced. If, however, the stenosis is only mild, the decision regarding valve replacement is much more difficult. Predicting when the aortic stenosis will progress rather rapidly is imprecise. We tend to make the decision on the basis of the peak transvalvular gradient. If it is >30 mm Hg, then the valve is replaced at the time of the coronary bypass. It is unclear what to recommend in patients with milder degrees of stenosis. The stenosis in patients with heavily calcified aortic valves tends to progress more rapidly than in those with only mildly calcified valves. Thus, assessing the quantity of calcific deposits on the valve in a patient with a low gradient may be helpful.

Beyond these 3 criteria for surgery (symptoms, left ventricular dysfunction, and patients undergoing coronary bypass surgery), the other criteria for aortic valve replacement are a little bit looser: IIA and IIB indications. I'm not sure how many of these we are going to keep in the next revision of the guidelines because it's not clear how helpful they are. One is the blood pressure response to exercise. Another factor is the degree of left ventricular hypertrophy. Runs of ventricular tachycardia by Holter monitoring may also tilt the decision toward valve replacement.

WCR: *When we were both at NIH, peak systolic gradients >80 mm Hg in patients with aortic stenosis were common. Today, I rarely see an operatively excised stenotic aortic valve with a peak gradient*

>80 mm Hg. The severity of the stenosis now is certainly less than it was in the 1960s and 1970s.

Let's move to mitral regurgitation. The indications for mitral valve operation in patients with mitral regurgitation secondary to left ventricular ischemia or infarction must be considerably different from those resulting from nonischemic mitral regurgitation. Your comments?

ROB: It's an easier discussion and more difficult in the same breath because the physiology differs so much depending on etiology. Is the mitral regurgitation secondary to cardiomyopathy? Is it secondary to myocardial ischemia, in which case left ventricular dysfunction is always present? Patients with left ventricular dysfunction do poorly no matter what you do. The operative approach is also unclear in those patients. They represent a high-risk group with bad outcomes because outcome is influenced primarily by the left ventricular dysfunction whether or not the mitral valve is replaced or repaired.

Let us focus on the conditions in which the valve itself causes the mitral regurgitation. Mitral valve prolapse is the major cause in this country of mitral regurgitation secondary to valve disease, and the mitral valve can often be repaired rather than replaced in this circumstance. The reason I said the decision is both easy and difficult is that it's been suggested that since the valve can usually be repaired, the threshold for operation should be lowered. Thus, the argument is that operation might be indicated for severe mitral regurgitation alone in the absence of symptoms. The analogy that is often made is atrial septal defect, which can be repaired successfully with low risk. We prevent the complications of atrial septal defect in later life by closing the defect in all patients in early life. The problem here is that in this country most patients with mitral regurgitation secondary to mitral valve prolapse end up having mitral valve replacement rather than repair!

The outcome of mitral valve repair is not reported in every center. The reports we see are from those centers that get great results—mainly the large centers with large volumes of patients. Establishing guidelines when results of surgery vary so much from one center to the next can be a problem. Do we set the lowest or highest common denominator? Should every patient with severe mitral regurgitation be referred for operation if repair can be performed? Or, do we not operate unless there are symptoms or evidence of declining left ventricular function or pulmonary hypertension or some other objective parameter? If we do that, then we tie the hands of those centers that are leading the field and perhaps showing what we could and should achieve. We don't want the guidelines to imply that these centers are doing things they shouldn't be doing because actually they may be setting new standards for the rest of us. We're going to try to make that point in the revision. If your center can achieve excellent results in individual patients based upon your own track record, and you know you can achieve a satisfactory repair with a very high likelihood, then maybe it's okay to recommend an early repair in a patient with severe mitral regurgitation. But, that action is appropriate only if you can achieve those superb results.

WCR: *One of my children is a cardiovascular surgeon, and he tells me that the average cardiovascular surgeon in the USA does about 10 valve replacements or repairs a year. Doing only 10 valve operations a year, the surgeon could not be comfortable doing either procedure, much less repair. You're talking about centers where the*

average surgeons do 100 valve operations a year and therefore become good at the repair procedure.

ROB: That's absolutely right. It's a difficult issue, but I think each physician has an absolute obligation to do what's best for each patient independent of the physician's referral pattern and location. In our program in Chicago, we have had a couple of different surgical teams since I've been there. We had a great surgeon who did terrific valve repairs but he left for personal reasons. We were left for a while without a surgeon who could repair valves, and consequently I referred some patients to other institutions. Then, we recruited successfully and now we perform superb valve repairs again at the medical center in which I work. Those out-referring decisions are difficult because we all want to be loyal to the team we work with day in and day out. But, we must do what is best for every patient.

We have difficulty writing guidelines for cardiologists as well as cardiac surgeons who see relatively few patients with valve conditions. Surgeons need sufficient volume to be proficient at both valve replacement and repair, but more so with the latter than the former. We have not achieved uniform standards nationwide on the surgical side on this point, nor do we have uniform standards regarding when to recommend valve repair. I've followed patients for over a decade now who have got enough mitral regurgitation that some centers undoubtedly would have operated on them 10 years ago, and they're still doing fine.

WCR: Braunwald used to say that if you're going to have one valve lesion then mitral regurgitation is the best one to have because it is more compatible with long-term survival than the other left-sided valve lesions. What do you know about the edge-to-edge operation for mitral regurgitation?

ROB: That's another Pandora's box. That's the procedure in which the posterior and anterior leaflets are brought together in the central portion of the mitral orifice, and it results in a double-orifice mitral valve. A mitral annular ring is also usually inserted at the same time. That procedure is not the one of choice because it usually results in some residual mitral regurgitation. It is not good to leave any mitral regurgitation behind, as a number of surgical series indicate that any degree of residual mitral regurgitation after repair puts a patient at higher risk of needing a second operation over the next 5 to 10 years.

WCR: Are any good follow-up studies available on that procedure postoperatively?

ROB: No. There are no reproducible results on that procedure as there are with other types of mitral repair. This procedure is now being done via the percutaneous route using an investigational device at a few centers. The percutaneous procedure worries me because once it gets in the community it's going to be even more difficult to put a break on the excitement about this new opportunity for intervening in patients, some of whom may not need intervention at all. Another worry is that if the edge-to-edge procedure is ineffective, it may prevent a more definitive repair procedure from being done later. Before these new devices get approved, careful scrutiny is needed as well as long-term clinical trials to be sure they are effective. The edge-to-edge procedure may be helpful in a patient who's very sick and potentially could not tolerate a long operation.

WCR: It's my understanding that most people with mitral valve prolapse, at least in the USA, are women. Of those persons with mi-

tral valve prolapse who die suddenly, most are women. The ones who develop enough mitral regurgitation to warrant mitral valve repair or replacement, however, are mostly men. Why is that?

ROB: That's my impression too. I agree with you. The people who get into trouble and develop endocarditis, ruptured chordae, or mitral regurgitation are mainly men >45 years of age. Men in that age group tend to have more severe myxomatous changes. I don't know why that is. There may be a genetic polymorphism that is more common in men, or maybe other factors influence the phenotypic expression of mitral valve prolapse in men and not in women.

WCR: Let's say your daughter had mitral valve prolapse at age 20. What would be your recommendations to her in an attempt to prevent any mitral operation years later? What can be done to slow its progression?

ROB: I'm not aware of anything to slow its progression.

WCR: You would certainly want to make sure her blood pressure stays down.

ROB: Oh, yes. Blood pressure is important. We certainly want to control hypertension if present.

WCR: In a nutshell, when would you recommend operative intervention in patients with mitral stenosis unassociated with aortic valve disease?

ROB: When patients have symptoms or develop pulmonary hypertension. Balloon valvulotomy is a good procedure for patients with no or minimal calcific deposits in the valve and no or only mild mitral regurgitation.

WCR: Why do you think atrial fibrillation occurs more frequently in patients with mitral stenosis than in patients with mitral regurgitation secondary to mitral valve prolapse?

ROB: That's a good question because the atria tend to be quite big with both. I don't know the answer. Atrial fibrillation clearly is a devastating component of mitral stenosis. I guess I would put that into my equation also, getting back to my indications for balloon valvulotomy. If the patient is a candidate for a balloon valvulotomy and the patient is having atrial fibrillation, I might move earlier. As mitral stenosis is almost always the result of rheumatic heart disease, it may be that inflammation or scarring of the atrial wall increases susceptibility to atrial fibrillation. What do you think?

WCR: I think rheumatic heart disease involves the atrial wall. Inflammation may be present during acute rheumatic fever, but later the amount of fibrous tissue, mainly occurring between myofibers, in patients with chronic mitral stenosis is considerable. Patients with mitral valve prolapse have essentially normal atrial walls.

I certainly agree that the expertise among both cardiologists and cardiac surgeons regarding cardiac valve disease is less now than in the past. Surgeons now are doing fewer valve operations during their training, and, therefore, they are not good valve surgeons upon completion of their training.

ROB: Yes, it's a real problem.

WCR: With so many cardiologists, the expertise is being diffused.

ROB: Yes, I agree. This is an area that requires more attention in our educational and training programs.

WCR: Bob, thank you so much. I really appreciate your coming to BUMC. You did a fantastic job.

ROB: Thank you, Bill.

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