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The Natural History and Hemodynamic Assessment of Aortic Valve Disease

Blase A. Carabello

East Carolina Heart Institute, Brody School of Medicine, and Vidant Medical Center, East Carolina University, Greenville, NC, USA

Aortic Stenosis

1. What are the causes of aortic stenosis (AS)?

In the developed world, calcification of the aortic leaflets is the most common cause of aortic stenosis (AS). Once thought to be a degenerative process, it is now clear that AS is due to active inflammation, with increased temperature of the areas affected. Those same areas demonstrate lymphocyte infiltration that leads to a calcified plaque similar to that of atherosclerosis. Indeed, the development of AS has many of the same risk factors associated with coronary disease. About 1% of the population is born with a bicuspid rather than a tricuspid aortic valve. When such patients develop AS, it occurs about 10–15 years earlier than in patients with tricuspid aortic valves. Earlier onset of disease may occur due to increased valve leaflet shear stress or to genetic abnormalities that lead to earlier calcification. The bicuspid valve may also be associated with proximal aortic root dilatation. Because calcific AS is an inflammatory process, it is also a progressive one. The rate of AS progression is remarkably variable, ranging from little progression year to year in some patients to an increase in aortic gradient by as much as 15 mmHg/yr in others.

Worldwide, rheumatic heart disease is still a major cause of AS. Congenital AS, chest irradiation, exposure to serotonergic drugs, and/or carcinoid disease and ochronosis are rarer causes of AS.

2. How is AS severity graded?

AS is graded as mild, moderate, or severe based upon the aortic valve area (AVA), aortic jet velocity, mean transvalvular gradient, and AVA indexed for body surface area (Table 1.1). Most importantly, the assessment of AS severity should not be based upon a single criterion. Rather, physical exam findings, the echocardiographic appearance of the aortic valve, jet velocity, gradient, valve calcium score, and valve area should be integrated into the overall assessment. This is especially true in low flow conditions, which reduce the gradient and jet velocity, making valve area, a calculated instead of directly measured value, more important but potentially less reliable.

3. What are the hemodynamic consequences of AS?

The normal AVA is about 3 cm^2. Reducing AVA to half its normal orifice creates little obstruction to flow, resulting in only a 10 mmHg gradient transvalvular at rest. However, further reductions in AVA cause a progressively greater LV pressure increase needed to drive blood past the obstruction. Thus for a valve area of 1.0 cm^2, the usual resting gradient is 25 mmHg; for an AVA of 0.75 cm^2, the gradient is about 50 mmHg; and for an AVA of 0.5 cm^2, the gradient could reach 100 mmHg. The increased gradient increases LV afterload, resulting in the development of concentric left ventricular hypertrophy, which results in both compensatory and pathologic consequences.

4. How are the hemodynamics of AS translated into symptoms?

The classic symptoms of AS are angina, syncope, and dyspnea on exertion (or other symptoms of heart failure). The onset of symptoms dramatically changes the prognosis of the disease, from a nearly normal mortality rate to a

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Table 1.1 Decision-making in patients with severe aortic stenosis (AS).

Class I indications for aortic valve replacement

1) Severe symptomatic AS

"Severe" defined as an integration of the following criteria (not all need to be present).

A. Transaortic jet velocity of >/=4 m/s
B. Mean valve gradient of >/=40 mmHg
C. Aortic valve area (AVA) of </=1.0 cm^2
D. Aortic valve area index </=0.6 cm^2

(When criteria are discordant, a valve calcium score may be helpful, with a score of >/=2000 au for men and >/=1200 au for women suggesting severe disease.)

(In low flow (stroke volume </=35 cc/m^2) low ejection fraction (EF) patients, augmentation of stroke volume by dobutamine infusion to calculate AVA at higher flow may be helpful.)

2) Severe asymptomatic AS with LV dysfunction (EF </=50%)

Class IIa indications for AVR

1) Very severe (jet velocity >/=5 m/s or AVA </=0.6 cm^2) asymptomatic AS
2) Asymptomatic patients with a positive exercise tolerance test (unable to achieve 75% of expected workload or failure of systolic pressure to increase with exercise)
3) Brain natriuretic peptide level >/=3× normal for patient's age and sex
4) Rapid worsening of AS with AVA reduction of >/= of 0.3 cm^2/yr

Transcatheter valve replacement (TAVR) preferred over surgical (SAVR) replacement

1) High risk or inoperable patients
2) Age >/=80

Surgical valve replacement preferred over TAVR

1) Age <65 in low risk patients

In all other groups, the decision for TAVR vs. SAVR should be made by a multidisciplinary Heart Team that includes patient preference

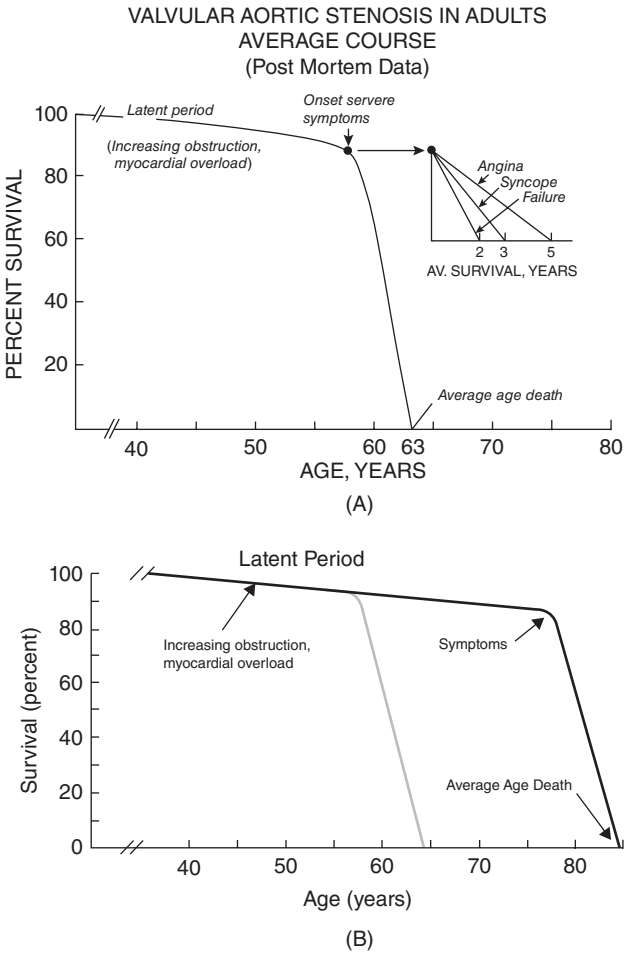

Figure 1.1 The natural history of AS. (a) The original natural history according to symptom onset as compiled by Ross and Braunwald. (b) A more contemporary natural history, reflecting the change in etiology over the past half-century. *Source:* Carabello, B.A. (2013). Compendium: introduction to aortic stenosis. *Circ. Res.* 113 (2): 179–185 / American Heart Association.

mortality rate of about 2%/mo. Thus about 75% of symptomatic patients die from AS in three years unless aortic valve replacement (AVR), the only effective treatment, intervenes (Figure 1.1). All three symptoms are related to the development of left ventricular hypertrophy (LVH).

Wall stress, the afterload on the myocardium, is defined by the formula for Laplacian stress (σ) = P×R/2h, where P = LV systolic pressure, R = LV radius, and h = LV thickness. It is generally held that the increased LV pressure caused by the transvalvular gradient in the Laplace numerator is compensated by LVH, which increases thickness in the denominator. Unfortunately, LVH brings with it pathologic consequences despite this compensation. Coronary blood flow is impaired by LVH, as LVH reduces myocardial capillary density, in turn potentiating myocardial ischemia and in part contributing to angina. Concentric hypertrophy reduces LV diastolic volume and LV stroke volume, reducing cardiac output. This potentiates a fall in blood pressure when peripheral resistance falls during exercise, leading to exercise-induced syncope. Hypertrophy eventually leads to LV systolic dysfunction through several mechanisms including abnormal calcium handling, apoptosis, ischemia, and cytoskeletal proliferation. Hypertrophy also causes increased LV stiffness, leading to diastolic dysfunction.

5. How are the hemodynamics of AS translated into physical exam findings?

AS is often first discovered when the provider auscults a murmur during physical examination. This systolic ejection murmur is typically a harsh raspy sound that radiates to the neck. In some cases, it also radiates to the LV apex,

giving the false impression that a second murmur, that of mitral regurgitation (MR), is also present (Gallavardin's phenomenon). If by chance the patient sustains an extra systole during the exam, the murmur intensifies after the pause as stroke volume increases, an increase that does not occur in MR. As AS severity worsens, the murmur peaks progressively later in systole until, in severe AS, peak intensity occurs just before S2. Palpation of the hypertrophied LV finds the LV apex beat sustained and forceful, while at the same time, aortic valve obstruction causes the carotid upstrokes to be delayed and weakened in quality (parvus et tardus). The finding of a forceful apical beat with simultaneously weak carotid upstrokes is an important clue that obstruction, AS, lies between the LV and the carotids. Because the aortic valve motion is reduced, the second heart sound may become single because only the P2 component is heard. However, this finding is less common today because AS is detected earlier in its course when the disease is less severe than it was in the pre-echo era.

6. How is AS diagnosed (imaging and invasive hemodynamics)?

When physical examination has led to suspicion of AS, echocardiography is employed as the key diagnostic tool. Echocardiography with Doppler interrogation of the valve provides data about LVH, LV function, valve movement, and severity of disease. Since the bloodstream must accelerate to maintain flow through the narrowed valve orifice, jet velocity must increase as the orifice becomes narrowed (Figure 1.2). Flow = area (A)× time-velocity integral (TVI), and flow must be maintained on both sides of the stenotic valve. Thus A_1 (outflow tract)×TVI_1 = A_2 (AVA)×VTI_2. Rearranging the terms, $A_2 = A_1 \times VTI_1/VTI_2$, calculating AVA by this continuity equation. As noted earlier, no single echo parameter should be used to assess AS severity. Rather, all data are taken together to arrive at a final assessment. Because AS is a progressive disease, patients should be followed by a yearly physical exam. For mild AS, echocardiography should be repeated every two to three years; for moderate AS, echocardiography should be performed yearly.

In some cases, the severity of AS is still in doubt following echocardiography. When this occurs, direct invasive gradient measurement is obtained at cardiac catheterization (Figure 1.3) and related to cardiac output to obtain AVA calculated by the Gorlin formula, where AVA = cardiac output/$\sqrt{}$ mean gradient.

7. What is low-flow AS?

The transvalvular gradient is created by the stroke volume passing through the valve. However, two conditions reduce stroke volume, causing the jet velocity and gradient to be reduced, potentially leading to an underestimation of AS severity. Systolic dysfunction reduces ejection fraction (EF) and stroke volume, in turn reducing gradient, a situation often referred to as "classic" low flow, usually defined as stroke volume <35 cc/m^2. In other cases, EF remains normal, but severe LVH reduces LV cavity size, in turn reducing LV stroke volume, often referred to as "paradoxical" low flow AS. Because both conditions reduce gradient and

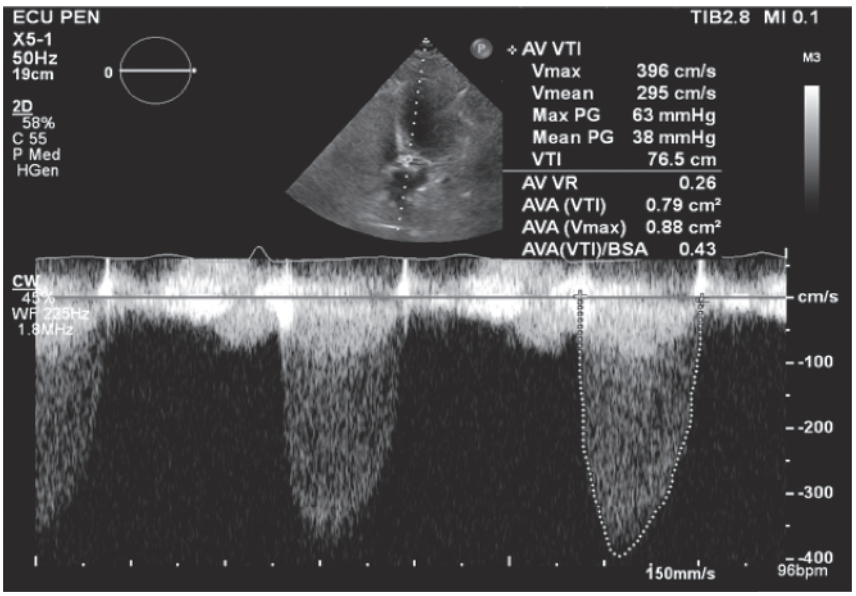

Figure 1.2 The transaortic Doppler jet in a patient with AS. Jet velocity is approaching 4 m/s, a criterion for "severe" AS.

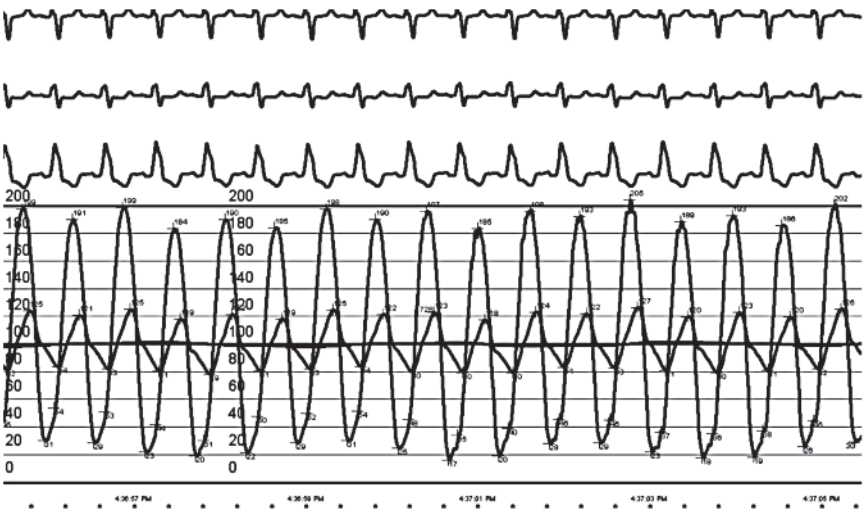

Figure 1.3 The transaortic pressure gradient in a patient with severe AS.

jet velocity, those parameters become unreliable in assessing AS severity, placing more weight on the valve area, itself subject to measurement errors. In such cases, valve calcium scoring adds additional data wherein scores >2000 Agatston units (au) for men and >1200 au for women suggest that AS is severe.

8. What are the indications for medical therapy of AS, and what do those therapies consist of?

There are no known effective therapies for treating AS. Attempts to reduce the progression of the disease with statin drugs have failed. However, as the disease typically occurs in older patients where systemic hypertension is present, hypertension is treated cautiously with standard antihypertensive therapy.

9. What are the indications for mechanical therapy of AS, and what do those therapies consist of?

AVR is indicated when the classic symptoms of angina, syncope, or dyspnea occur in patients with severe disease (Table 1.1). The occurrence of LV dysfunction (EF < 50%) even in asymptomatic patients is also an indication of AVR. Occasionally, patients with borderline moderate/severe AS may develop symptoms although they technically do not meet "severe" criteria. Because symptoms are subjective in nature, corroborating evidence obtained from exercise testing and biomarkers helps tip the decision in favor of AVR if they are abnormal. AVR may be considered in asymptomatic patients with very severe AS, i.e. those with a jet velocity of >/=5.0 m/s or AVA </=0.6 cm^2 and in patients with a progressive fall in EF toward 50%.

AVR can be performed percutaneously by catheter technique (transcatheter aortic valve replacement [TAVR]) or surgical implantation (surgical aortic valve replacement [SAVR]). TAVR is obviously less invasive and has lower implantation mortality and lower stroke risk than SAVR in most patients. However, because the durability of TAVR is unknown, it is recommended for patients of all risk categories >/=80 years of age and not recommended for low-risk patients </=65 years old, with risk and procedure recommendations for patients aged 65–80 determined by clinical judgment. Surgery is also more apt in cases where additional heart diseases not addressed by TAVR must be considered. In all cases, judgment about which procedure is appropriate should be discussed by a multidisciplinary Heart Team that strongly considers patient preference.

10. What is the prognosis for AS?

As noted earlier, the prognosis for symptomatic patients without AVR is dismal, with only a 25% three-year survival rate. For patients aged 50–65, AVR adds approximately 15 years to their lifespan.

Aortic Regurgitation

11. What are the major etiologies of aortic regurgitation (AR)?

Aortic regurgitation (AR) occurs when the aortic leaflets fail to coapt either due to inherent pathology of the leaflets themselves or due to dilatation of the aortic root, pulling

Table 1.2 Decision-making in patients with severe aortic regurgitation (AR).

Class I indications for aortic valve replacement
1) Severe symptomatic AR
"Severe" defined as an integration of the following criteria (not all need to be present)
E. Regurgitant jet fills >/=65% of left ventricular outflow tract
F. Vena contracta >/=0.6 cm^2
G. Regurgitant volume >/=60 cc/beat
H. Holodiastloic reversal of abdominal aortic flow
2) Severe asymptomatic AR with LV dysfunction (EF </=55%)
Class IIa indications for AVR
1) Left ventricular end systolic dimension >/=50 mm

the leaflets away from their coaptation point. Leaflet pathologies include infective endocarditis, rheumatic valve disease, bicuspid aortic valve, myxomatous valve degeneration, serotonergic drugs, carcinoid syndrome, trauma, radiation, collagen vascular disease, and non-infectious endocarditis. Aortic root causes include aortic dissection, hypertension with root dilatation, Marfan syndrome, Ehlers–Danlos syndrome, Loeys Dietz syndrome, ankylosing spondylitis, syphilis, and giant cell arteritis.

12. How is severe AR defined?

Several parameters are incorporated into the assessment of AR severity and are listed in Table 1.2.

Chronic AR

13. What are the hemodynamics of chronic AR?

As AR severity worsens, the LV progressively dilates, increasing total stroke volume, compensating for the volume regurgitated back into the LV during diastole. This produces a hyperdynamic circulation. Because pulse pressure increases with increasing stroke volume, pulse pressure widens; diastolic pressure falls due to diastolic runoff into the LV, while systolic pressure increases caused by the increase in stroke volume. Thus AR is a combined pressure and volume overload, causing both eccentric and concentric LVH. Afterload in AR can be as high as that seen in AS, the more typical pressure overload lesion. In very severe AR, end diastolic aortic pressure and end diastolic LV pressure may become equal (Figure 1.4).

14. How are chronic AR hemodynamics translated into symptoms?

The typical symptoms are those of heart failure, including dyspnea on exertion, orthopnea paroxysmal nocturnal dyspnea. Occasionally, the low systemic diastolic pressure may reduce coronary blood flow, causing angina or reducing cerebral perfusion, leading to syncope. Rare symptoms include flushing, carotid pain, and an uncomfortable awareness of the heartbeat.

15. How are chronic AR hemodynamics translated into physical signs?

The hemodynamics of severe chronic AR produce one of the most dynamic physical exams in cardiology. The enlarged LV that develops to compensate for the regurgitant volume displaces the apical beat downward and to the left. It is often very noticeable upon inspection and easily palpable. The murmur of chronic AR is a diastolic blowing sound best heard with the patient sitting up and leaning forward. In severe AR, the murmur may become holodiastolic. The diastolic jet of AR may impinge upon the mitral valve, partially closing it in diastole and also causing it to vibrate, leading to a rumbling murmur similar to that of mitral stenosis (Austin Flint murmur).

As noted earlier, there is a large total stroke volume and widened pulse pressure that together produce a myriad of clinical signs. There is a rapid, forceful carotid upstroke with a brisk decline (Corrigan's pulse). Compression of the nails finds systolic plethora and diastolic blanching of the nail bed (Quinke's pulse). One may observe bobbing of the head in cadence to the heartbeat (de Musset's sign) or a to-and-fro bruit in the femoral artery when compressed by the bell of the stethoscope (Duroziez' sign). There may be systolic augmentation of the leg blood pressure compared to the arm by >/=40 mmHg (Hill's sign).

16. How is AR diagnosed (imaging and invasive hemodynamics)?

As with all valve lesions, transthoracic echocardiography (TTE) is the mainstay of diagnosis. This tool can visualize the aortic root and valve in helping to define the mechanism for the AR. TTE can quantitate the severity of AR and its effects on LV chamber size as well as LV function (Table 1.2).

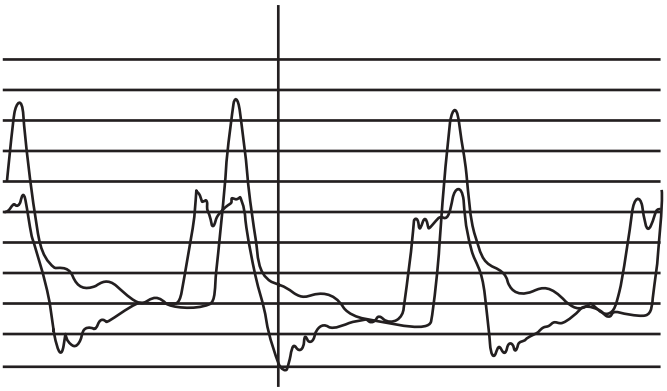

Figure 1.4 Pressure tracing from a patient with severe acute AR, demonstrating the rapid increase in LV diastolic pressure and diastasis between aortic and LV pressures.

TTE is ideal for following the progression of AR longitudinally.

If TTE images are non-diagnostic, cardiac MRI can precisely measure regurgitant volume and regurgitant fraction, LV volume, and LV EF, parameters useful in deciding upon AR therapy.

In some cases, invasive hemodynamics, especially during exercise, may help to clarify discordant resting findings, and aortography may also be helpful in grading AR severity.

17. What are the indications for medical therapy in AR and of what do Those therapies consist?

AR is a mechanical problem, the definitive therapy for which is also mechanical, i.e. AVR. Because afterload is increased in AR, attempts have been made to reduce afterload with vasodilators in the hope of increasing forward flow, in turn decreasing regurgitant flow. These efforts have not produced conclusive results. Currently, the only medical therapy is for standard treatment of systolic hypertension, which often accompanies AR.

18. What are the indications for mechanical therapy of AR and of what do Those therapies consist?

The definitive therapy for AR is AVR. Transcatheter AVR employs the annular calcium present in AS for securing the valve in place. In AR, annular calcium is not dense enough to prevent valve embolization, so the technique is not apt for this lesion. Occasionally, valve repair instead of replacement can be performed by surgeons experienced in this technique.

Because the onset of either symptoms or LV dysfunction worsens prognosis, AVR should be performed at the onset of symptoms or when LV EF Becomes <55% or when end systolic dimension (ESD) >/=50–55 mm. Some authorities would recommend AVR at a smaller ESD if there has been a progressive increase in ESD or a progressive decrease in LV EF.

When AR has been caused by a bicuspid aortic valve, it is often accompanied by dilatation of the aorta itself. Debate continues as to whether this dilatation is due to a genetic abnormality or is due to abnormal turbulent flow impinging on the aorta as the flow exits the valve. In any case, the aortic should be prophylactically replaced at the time of AVR if the aortic diameter exceeds 45–50 mm.

19. What is the prognosis following treatment

Because most patients with AR are in their 50s or 60s when they require AVR, the risks inherent to prosthetic valves reduce life span so that, on average, if AVR has occurred in a timely fashion, the life span is approximately 15 years after implantation.

Severe Acute AR

Severe acute AR as might occur in aortic valve infective endocarditis is often a life-threatening emergency. Unlike in chronic AR, there has been no time in acute AR for compensatory hypertrophy to develop. Accordingly, there is a dramatic fall in forward cardiac output with a concomitant increase in left ventricular (LV) and left atrial (LA) filling pressure, leading potentially to cardiogenic shock and pulmonary edema. Despite these extreme hemodynamic

abnormalities, the patient's physical examination may be misleadingly unremarkable. The rapid rise in LV diastolic pressure (Figure 1.4) limits the transaortic pressure gradient driving the AR so that the murmur may become short and unimpressive. High diastolic filling pressure may close the mitral valve prior to systole, causing S1 to be soft in intensity. All of the signs noted in chronic AR are usually absent because the LV volume is not increased so that the increased total stroke volume and wide pulse pressure causing those signs are also absent. Often, subtle changes in symptoms and vital signs such as mild orthopnea and tachycardia may be the only clues that decompensation is occurring.

Once acute AR is suspected, or if unexplained decompensation occurs in the face of infective endocarditis, TTE is indicated, usually accompanied by transesophageal echocardiography. Severe AR, especially if accompanied by mitral valve pre-closure, is an indication of early AVR. While there may be concern about infection of the AVR, this is in fact rare, occurring in only about 5% of cases.

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