EDITORIAL COMMENT
Afterload Reduction in Chronic Aortic Regurgitation
It Sure Seems Like a Good Idea*

Thomas M. Bashore, MD, FACC†
Durham, North Carolina

“The beginning of knowledge is the discovery of something we do not understand.”

Frank Herbert (1920 to 1986) (1)

In this issue of the Journal, Scognamiglio et al. (2) from Padua, Italy, follow up their prior observation on the value of afterload reduction in patients with aortic insufficiency (AI) and normal left ventricular (LV) function (3) by reporting on those that developed LV dysfunction before surgery.

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Their initial study revealed that AI patients pretreated with nifedipine (compared to digoxin) did much better after aortic valve replacement (AVR). Concerns regarding short-acting nifedipine, though, have resulted in mostly alternative afterload reducing agents being used. This has occurred despite essentially no data on how much to use and whether the practice should be continued postoperatively. This strategy of afterload reduction is supported by the American Heart Association/American College of Cardiology Task Force on the valvular disease and is incorporated into their recent guidelines (4).

In the authors’ current randomized trial, they observe that, while the nifedipine-pretreated group is similar to the nontreated group in regard to LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and ejection fraction (EF) going into surgery, they are not after AVR. This pretreatment effect becomes even more evident at the 5-year and 10-year anniversaries after AVR (presumably despite no further treatment with nifedipine). The implication is that nifedipine afterload reduction does something good that persists long after the AI is resolved, even in those with an abnormal ventricle.

THE EFFECT OF AI ON VENTRICULAR FUNCTION MEASUREMENTS

Aortic insufficiency results in increased preload or diastolic wall stress (due to the volume overload) and increased afterload or systolic stress (due to the ejection of blood into the high-impedance aorta). Peripheral vascular tone, aortic compliance, viscoelasticity, blood inertia, and reflected waves all contribute to the latter (5). Myocardial hypertrophy develops in response to systolic wall stress by the Laplace relationship (pressure \(\times\) radius/2 \(\times\) wall thickness). In response to the increased diastolic stress, sarcomeres replicate end-to-end to handle the extra volume. This increases systolic wall stress and results in further hypertrophy to return systolic stress back to normal. Because the chamber is large relative to wall thickness, this process has been termed “eccentric” hypertrophy. In the compensated state, contractile function remains preserved. Eventually, though, myocardial failure ensues via a series of complex events that include changes in the myocyte phenotype due to re-expression of fetal genes, cellular apoptosis, alteration in the expression or function of contractile proteins, changes in the extracellular matrix, and abnormalities in cellular energetics (6).

Patients remain asymptomatic for long periods. Symptoms usually emerge when diastolic dysfunction occurs. Unfortunately, systolic dysfunction invariably precedes diastolic dysfunction in chronic AI. Determining when systolic dysfunction has occurred then becomes the key to following these patients. Because AI alters the loading conditions, commonly used measures, such as the EF, poorly reflect the contractile state. The simplest way to understand all this clinically is to examine the effect of AI on the pressure-volume relationship and note what happens when contractility decreases. In Figure 1, the normal pressure-volume relationship is represented by a box. The limits of the box represent the ESV and EDV; the width is the stroke volume. The EF is simply the width of the “box” divided by the EDV. Each beat of the heart is represented by this “box” and resides nestled between a line of “systolic contractility” (similar to Emax) and a line of “diastolic compliance.” At any level of contractility and compliance, the heart beats merrily away within these confines. The calculated EF provides only a surrogate for a better surrogate (Emax) that is itself a surrogate for contractility in the intact heart.

Figure 2A schematically shows what happens in AI. Despite no change in the line of contractility, increased afterload makes the “box” higher, the ESV greater, the box width more narrow, and the EF lower. Increased preload makes the EDV greater, the width of the box (SV) larger, and the EF higher. Because the increased preload is a much bigger deal in AI than the afterload, the result is a relatively normal or slightly increased EF in most AI patients.

As contractility declines (Fig. 2B), the slope of the line of “contractility” drops resulting in the pressure-volume “box” getting narrower (lower EF) and the ESV getting larger. The most important measures to follow are, thus, the ESV (or dimensions) and the EF. This simple concept has been used over the years to help decide operability in AI and remains valid to this day. It is now generally accepted that LV end-diastolic dimension of <65 mm and an EF of

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†Duke University Medical Center, Durham, North Carolina.
>55% represents the compensated state, while end-systolic dimensions of >50 mm or an EF <50% represents decompensation even in asymptomatic patients (4).

Earlier attempts at defining early LV systolic dysfunction in AI patients addressed exercise reserve, usually with radionuclide angiography. However, tachycardia reduces diastolic time and the regurgitant volume per beat, making interpretation of exercise EF difficult at best. Inadequate hypertrophy may also be reflected by an increase in end-systolic wall stress (ESS), but measures of this have been met with little enthusiasm. Combining exercise EF and stress measurements, Borer et al. (7) examined the decrement in the change of EF per unit of exercise-induced increment in ESS and found this measure superior to LVEF or ventricular sizes in picking out those likely to develop heart failure. Unfortunately this valiant effort has not caught on clinically either. So we are pretty much stuck with using the resting EF and ESV measures. Fortunately, as a recent editorial noted, when contractility indexes are not measured, the LV end-systolic dimension still emerges as the best prognostic indicator (8).

Figure 1. The mathematics of the ejection fraction. The normal pressure-volume loop is represented as a box that is confined by a line of contractility and a line of diastolic compliance. The ejection fraction (EF) is simply the width of the box (stroke volume [SV]) divided by the left ventricular end-diastolic volume (LVEDV). EDV = end-diastolic volume; ESV = end-systolic volume. AC = aortic closure; AO = aortic opening; MC = mitral closure; MO = mitral opening.

Figure 2. The effect of aortic insufficiency (AI). (A) Compares AI to the normal. In AI the pressure-volume “box” is wider due to the volume overload and taller due to the afterload increase. These increase end-systolic (ESV) and end-diastolic (EDV) volumes. The overall ejection fraction (EF) is generally elevated. In (B), as the slope of the line of contractility drops, the ESV has to rise, and the EF has to fall.

How does nifedipine make all this better?

How pretreatment with nifedipine improves the outlook for years after surgical intervention is unclear. The presumption is that this is somehow due to the consequences of afterload reduction. While the systolic blood pressures were elevated, there was no difference between the groups. Chronic afterload reduction with hydralazine, angiotensin-converting enzyme inhibitors, or other calcium channel blockers have been shown to reduce LV sizes and improve the EF, though short-term studies have not shown that hypertrophy is prevented (10).

In particular, why did nifedipine have a protective effect long after AVR? One can hallucinate a variety of thoughts, but none have much validity. Does the afterload reduction prevent irreversible changes in myocyte geometry or in the time from disease recognition to AVR. Other measured baseline factors (including a comorbidity index) were similar between the two groups except for age. Women are thought to have a similar operative risk after AVR, but a reduced 10-year survival. In this report, there are an equal number of women in each group. The authors also report an extremely low surgical mortality in these low EF patients (<1%). This is no small feat and flies in the face of other studies with an operative mortality of about 14% in this situation (9).

HOW DOES NIFEDIPINE MAKE ALL THIS BETTER?
extracellular matrix (11) that recovers after AVR? Or could there be something unique about the use of a calcium blocker? For instance, it is known that myocardial blood flow is altered in AI and improved after aortic valve replacement (12); might nifedipine simply be having a favorable effect on myocardial blood flow preoperatively that allows for even better perfusion and recovery of the myocardium postoperatively?

Though it seems unlikely, are the negative inotropic effects of nifedipine simply being removed when the drug is stopped after surgery? It has been demonstrated that chronic blockage of the myocardial calcium channels with nifedipine results in their upregulation (13).

It is known that sudden death from cardiac arrhythmias may be initiated by delayed afterdepolarizations that result from an aberrant sarcoplasmic reticulum calcium leak (14); might the improved survival related to the use of nifedipine be somehow related to improved calcium homeostasis within the myocardial cell itself? To date, there is little to support such as role, as nifedipine apparently has no action on the ryanodine sarcoplasmic reticulum receptor (15). In a very different setting, diltiazem has been reported to prevent cardiomyopathy in a mouse model of hypertrophic cardiomyopathy (16).

So why does this seem to work? In such a clinical observational study, the answers to these and other questions beg for an explanation. The results, however, are intriguing and important, and the authors are to be congratulated for pulling off a long-term study of this nature. Given the fact that the cardiology community has accepted the notion of afterload reduction in this setting, it is unlikely that a similar study will ever be funded using other afterload-reducing agents. That is a real shame, because we understand so little about what is going on. Their data do add a measure of comfort to our current practice, even if we remain clueless as to why the effect persists for such an extended time after AVR. Afterload reduction in AI sure seems like a good idea.

**REFERENCES**

1. The Quotations Page. Available at: http://www.quotationspage.com/