Severe aortic stenosis (AS) untreated by aortic valve replacement is a fatal disease with a 3-year mortality rate of 75% once the classic symptoms of the disease ensue.\textsuperscript{1-4} Approximately 15% of AS patients present with syncope, which is an ominous occurrence.\textsuperscript{2} Indeed, a master cardiologist and my former mentor, Dr Lewis Dexter, quipped that sudden death in AS was simply prolonged syncope. Although exercise-induced arrhythmia and/or a pressure-induced vasodepressor response have been invoked to explain syncope in AS, the most commonly held theory invokes Ohm’s law. This well-known principle states that $V=I\times R$, where $V$ is voltage, $I$ is current, and $R$ is resistance. Applied to the circulation, the terms are substituted such that $P=CO\times R$, where $P$ is pressure, $CO$ is cardiac output (L/min), and $R$ is the vascular resistance in the area of interest. The Figure diagrams the circulation in the patient with AS as having 3 major resistors: $R_1$, the total pulmonary resistance made up of left ventricular (LV) filling pressure plus pulmonary vascular resistance that governs LV filling; $R_2$, the resistance offered by the aortic valve; and $R_3$, the systemic vascular resistance (SVR). Pressure at these 3 points in the circulation is determined by the product of $CO\times R$. If resistance drops without a concomitant increase in output, pressure must also fall. In severe AS, it has been assumed that $R_2$ (valve resistance) exceeds $R_3$ (SVR) substantially. As such, a fall in SVR caused by exercise or by administration of a vasodilator would cause a fall in systemic pressure because $R_2$, the severely stenotic aortic valve, would block a compensatory increase in forward output causing systemic hypotension and syncope. Is this theory proven?

A study in this issue of Circulation addresses this issue. In a detailed hemodynamic analysis, Lindman et al\textsuperscript{5} present their findings on the effects of a single dose of sildenafil. The results were wonderfully complex and give enormous insight into the application of Ohm’s law to patients with AS. The present study is not the first to report the use of vasodilators in AS. Approximately 15% of AS patients present with syncope, which is an ominous occurrence.\textsuperscript{2} Indeed, a master cardiologist and my former mentor, Dr Lewis Dexter, quipped that sudden death in AS was simply prolonged syncope. Although exercise-induced arrhythmia and/or a pressure-induced vasodepressor response have been invoked to explain syncope in AS, the most commonly held theory invokes Ohm’s law. This well-known principle states that $V=I\times R$, where $V$ is voltage, $I$ is current, and $R$ is resistance. Applied to the circulation, the terms are substituted such that $P=CO\times R$, where $P$ is pressure, $CO$ is cardiac output (L/min), and $R$ is the vascular resistance in the area of interest. The Figure diagrams the circulation in the patient with AS as having 3 major resistors: $R_1$, the total pulmonary resistance made up of left ventricular (LV) filling pressure plus pulmonary vascular resistance that governs LV filling; $R_2$, the resistance offered by the aortic valve; and $R_3$, the systemic vascular resistance (SVR). Pressure at these 3 points in the circulation is determined by the product of $CO\times R$. If resistance drops without a concomitant increase in output, pressure must also fall. In severe AS, it has been assumed that $R_2$ (valve resistance) exceeds $R_3$ (SVR) substantially. As such, a fall in SVR caused by exercise or by administration of a vasodilator would cause a fall in systemic pressure because $R_2$, the severely stenotic aortic valve, would block a compensatory increase in forward output causing systemic hypotension and syncope. Is this theory proven?

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Previous Use of Vasodilators in AS

The present study is not the first to report the use of vasodilators in AS. Indeed, there are several reports of the use of angiotensin-converting enzyme inhibitors in severe symptomatic disease.\textsuperscript{7-9} A recent study randomized patients with symptomatic AS to receive placebo or enalapril.\textsuperscript{7} For the most part, enalapril was well tolerated without causing hypotension while the drug improved symptoms and increased performance on a 6-minute walk. However, 3 patients with LV dysfunction suffered hypotension and had to be withdrawn. When Ikram and colleagues\textsuperscript{10} treated 35 patients with severe AS with sodium nitroprusside, they also found a variable response. Fourteen patients had an increase in CO and 24 had a decrease. The latter group had lower LV filling pressures and presumably had a significant reduction in preload, leading
to the decrease in CO. Mean arterial pressure in the entire group fell from 99 to 80 mm Hg.

In another remarkable study, sodium nitroprusside was administered to AS patients with pulmonary edema during careful hemodynamic monitoring. The patients improved dramatically without induced hypotension. Although the drug reduced SVR, that change did not explain the outcome. Analysis of pressure-volume loops taken from the study patients indicated that nitroprusside increased contractility, a remarkable response for an agent not known to be a positive inotrope. It is likely that by reducing LV filling pressure, nitroprusside increased the pressure gradient driving subendocardial coronary blood flow, thus relieving subendocardial ischemia and improving the inotropic state.

AS: Then and Now
Severe untreated AS has been recognized as a fatal disease for decades, but its demographics have changed dramatically over time. Forty years ago, rheumatic heart disease and congenital AS were the most common causes of AS, leading to severe disease at a relatively early age. Forty years ago, Doppler echocardiographic interrogation of the aortic valve was not yet used, so patients with AS were often not detected until the disease was much more severe than when detected today. Aortic valve areas of <0.5 cm² were often found for the first time during cardiac catheterization and the so-called Carabello sign was observed (I rarely observe it today). In that era, the proscription against the use of vasodilators in AS was strongly espoused. Today, however, atherosclerotic calcific disease is the major cause of AS, and disease is detected noninvasively earlier in its course. The change in etiology has shifted the age of symptom onset to about 2 decades later in life. Aging in turn brings about vascular changes that make systemic hypertension the rule rather than the exception. Thus, R₃ is greater today that it was 4 decades ago, and R₂ is less. As in the Lindman et al study, the presence of hypertension and relatively less severe obstruction to LV outflow may protect patients from clinical hypotension. Although Lindman et al reported a 14-mm Hg drop in mean arterial blood pressure, the mean arterial blood pressure was still 94 mm Hg, and indeed the patients were hypertensive.

Phosphodiesterase 5 Inhibitors, AS, and Erectile Dysfunction: Can Vasodilators Be Used With Impunity in AS?

The answer to this question is a resounding “no.” In a patient with a slightly tighter valve, less ventricular reserve, or a lower LV filling pressure or a patient whose untreated mean arterial blood pressure is 70 mm Hg instead of 104 mm Hg, the use of any vasodilator could cause hypotension and or syncope. Furthermore, AS is a progressive disease, with R₂ becoming greater with time. Vasodilator therapy tolerated today may cause hypotension tomorrow when the stenosis is a little worse or the patient’s volume status has contracted from exercise, perspiration, etc. Although it is unlikely that sildenafil will be used in the near future to treat AS, the AS age group is also common to men with erectile dysfunction, the standard treatment of which includes sildenafil and other phosphodiesterase 5 inhibitors. Men on such therapy who also have AS should be apprised of the benefits and risks of such therapy and may wish to consider other erectile aids.

Conclusions
The safe use of vasodilators in some patients with severe AS is well documented, and the Lindman et al study adds to that literature, elegantly defining the hemodynamic changes accompanying sildenafil use. As noted, many patients with AS have a second fatal illness called hypertension that must also be treated, and the question about best therapy often arises. Worry that diuretics may decrease preload and that β-blockers may reduce the inotropy needed to drive blood past the stenotic valve raises the issue of vasodilator use. For symptomatic AS patients, the best course of action is, of course, aortic valve replacement. However, for the asymptomatic AS patient who requires antihypertensive therapy, we simply need to keep Ohm’s law in mind. Vasodilators can cause an increase in CO that helps offset the drop in SVR even in severe AS. Thus, vasodilators may be used with extreme caution to treat the hypertension that today commonly accompanies this common valve disease.

Disclosures
None.

References


**KEY WORDS:** Editorials • aortic valve stenosis • heart failure • phosphodiesterase inhibitors
Georg Ohm and the Changing Character of Aortic Stenosis: It's Not Your Grandfather's Oldsmobile
Blase A. Carabello

_Circulation_. 2012;125:2295-2297
doi: 10.1161/CIRCULATIONAHA.112.105825
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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