Systolic Ejection Murmurs in the Era of Modern Cardiology
What Do We Really Know?
JOSEPH P. MURGO, MD, FACC*
San Antonio, Texas

The basics of pulsatile ejection dynamics are reviewed in order to clarify the relationships among left ventricular and aortic pressures, intra-left ventricular and aortic flow velocities, and cardiovascular sound. The principles of turbulent flow are examined using the Reynolds number concept, and the evidence for cause-and-effect relationships between turbulent flow and murmur generation is presented. Examples of hemodynamics and phonocardiography are given for normal subjects and are compared to patients with aortic stenosis and hypertrophic cardiomyopathy. The concepts presented are used to analyze the results of a new study suggesting increased intraventricular velocities as a new cause for systolic murmurs in adults.

For many years clinicians have been challenged, in both the pediatric and adult population, with the differentiation of “innocent” or benign systolic murmurs from those associated with clinically significant pathology (1–9). In the last few decades, the prevalence of diseases that caused “classic” cardiac murmurs has changed. In countries with developed health care delivery systems, the treatment of ischemic and hypertensive heart diseases and their complications now dominates the care delivered by the modern adult cardiologist. Simultaneously, the advent and continued improvements of echocardiographic technologies have provided the most powerful tools to evaluate cardiovascular structure and function (10,11). Reliance on the physical examination, and particularly cardiac auscultation, for diagnosing the cause of cardiac murmurs has decreased (12–14).

In this issue of the Journal, Spooner et al. (15) describe the Doppler-echocardiographic findings and clinical characteristics of a group of patients specifically referred to a clinical echocardiographic laboratory for the evaluation of a systolic murmur. Their findings suggest that a significant percentage of patients do not have “recognizable” causes of murmurs, that is, valvular lesions, congenital defects or hypertrophic cardiomyopathy (HCM). Rather, their patients were characterized by the presence of increased intraventricular blood flow velocities that appear to be associated with a higher prevalence of hypertension, concentric left ventricular hypertrophy (LVH), increased ejection fractions and preserved regional wall motion. Qualitatively, some of the murmurs described occurred in mid- to late systole and responded to bedside maneuvers in a manner much like patients with HCM. Similarly, spectral velocity profiles, obtained by routine clinical laboratory techniques, are described with peak left ventricular (LV) velocities occurring in mid- to late systole, some with late-peaking “dagger-shaped” waveforms. The authors conclude that these previously “unrecognized” murmurs may not be benign or “innocent,” in that they are associated with hypertensive hypertrophic heart disease.

There are several limitations in the study by Spooner et al. (15). As the authors admit, they cannot prove a direct cause-and-effect relationship between increased intraventricular velocities and murmur generation. They point out that increased intraventricular velocities alone, except in HCM, are not a recognized cause of systolic murmurs, yet the majority of the velocity measurements that they report are of considerably lower magnitude than those found in HCM. Indeed, the study by Spooner et al. (15) raises the very issue of how well murmur generation is really understood in modern clinical cardiology.

In an attempt to provide additional insight into the meaning of their observations, the goals of this commentary are to 1) review basic LV and aortic pressure-flow relationships during ejection in normal humans to demonstrate that peak pressure gradients and peak flow rates may occur at different times during systole; 2) demonstrate that the peak intensity of systolic ejection murmurs is associated with the peak of flow rates, not pressure gradients; 3) show that the production of turbulent flow, necessary for the production of cardiovascular sound, is related, through the Reynolds number concept, to ejection flow rates and cardiovascular geometry; and 4) demonstrate these principles by examples of invasive hemodynamics and intracardiac phonocardiography in normal humans, aortic stenosis (AS) and HCM.

From the Heart and Vascular Institute of Texas, San Antonio, Texas.

Manuscript received July 20, 1998; accepted July 22, 1998.

Address for correspondence: Dr. Joseph P. Murgo, CEO/Medical Director, Heart and Vascular institute of Texas, 1935 NE Loop 410, San Antonio, Texas 78217. E-mail: jmurgo@txdirect.net.

©1998 by the American College of Cardiology
Published by Elsevier Science Inc.

0735-1097/98/$19.00
PII S0735-1097(98)00425-2
Intra-Left Ventricular Systolic Pressure-Flow Relationships in Normal Humans

Because ejection murmurs are often associated with substantial cardiovascular pressure gradients in the more commonly “recognized” causes for murmurs, some might question what magnitude of intracavitary gradients was generated in the study subjects of Spooner et al (15), particularly as there were several characteristics similar to patients with HCM. No attempt at measuring intracavitary pressure differences was made in their study. Using the modified Bernoulli equation (16) and the data reported, 95% of their patients with increased intra-LV flow velocities would not have generated gradients higher than those found in normal ventricles (17). However, systolic murmurs can occur in the presence of small, physiologic pressure gradients, and the timing, shape, and very origin of murmurs are directly related, as Spooner et al. (15) suggest, to blood flow velocity and cardiovascular geometry. This principle is best illustrated when peak instantaneous pressure gradients and peak flow velocities occur at different times during systole, as this discussion will show.

Figure 1 illustrates the presence of intra-LV pressure gradients in a subject with normal LV and valvular function. The electronically derived “pressure difference” signal, obtained by subtraction of the subaortic LV pressure from the LV pressure within the body of the LV, provides a detailed examination of the configuration, magnitude and time course of the intraventricular pressure gradient. A simultaneous LV flow velocity signal was recorded using an electromagnetic flow probe. A sinus beat, a premature ventricular contraction (PVC), and a subsequent sinus beat following a postcompensatory pause are shown. In both sinus beats, there is an early systolic pressure gradient that is rapidly generated between the body of the LV and the left ventricle outflow tract (LVOT). In this example, the peak instantaneous gradient is approximately 13 mm Hg, appears before the peak of aortic outflow and is more closely aligned with the maximum rise in the LV outflow waveform (i.e., peak dQ/dt = peak flow acceleration) (17). This discordant relationship between the timing of the peak gradient and the peak flow rate itself reminds us that the basic laws of inertial physics apply to the circulation. In mathematical terms, an oversimplified version of the unsteady Bernoulli equation gives the relationship between the pressure difference developed along a flow stream:

$$\Delta P = \frac{dQ}{dt} + \beta Q^2$$  \[1\]

where Q is the symbol for flow (cc/sec). The coefficients $\alpha$ and $\beta$ include blood density and geometric factors. There are two components on the right side of the equation. The first, labeled the local acceleration component, is the fluid dynamic version of Newton’s second law (force = mass $\times$ acceleration), and is associated with the forces developed in overcoming inertia (setting a bolus of blood, which has mass, into motion). This term is the least familiar to clinical cardiologists as it normally plays a small role in the more common pathophysiologic processes that result from various disease processes. The second term of the equation, labeled the convective acceleration component, is the result of blood flow through any area of the cardiovascular system where the effective cross-sectional area changes as a function of distance along the flow stream. Clinical examples would be valvular aortic stenosis and coarctation of the aorta (AO).

In a nonpulsatile flow system, the first term of equation 1 would drop out because dQ/dt, the rate of change of flow (acceleration), would be equal to zero. Conversely, in a straight, uniform pipe (or over short segments of the thoracic or abdominal AO), very little or no change in cross-sectional area occurs, and the second term can be ignored. In pulsatile blood flow in areas of the cardiovascular system where geometric change is negligible, the first term of the unsteady Bernoulli equation is the most dominant. In situations where marked geometric narrowing occurs (such as in aortic stenosis or coarctation), the second term of the equation dominates. The latter term is the most familiar to clinical cardiologists and, converting flow rate (cc/sec) to flow velocity (cm/sec), it becomes the popular “modified” Bernoulli equation used in clinical echocardiography laboratories (16). The local acceler-
ation component is ignored in the modified Bernoulli equation because the application of this equation in clinical settings is most always directed toward the evaluation of valvular or vascular obstructions, or estimates of chamber pressures generated by systolic regurgitant jets across closed or semiclosed atrioventricular valves. However, in normal cardiovascular systems, both components operate to varying degrees and, depending upon a variety of geometric and hemodynamic conditions, the local acceleration component could be substantial. In the study by Spooner et al. (15), local acceleration effects may well have generated intracavitary pressure differences beyond normal levels, but the data necessary to calculate such effects were not provided.

**Left Ventricular–Aortic Systolic Pressure-Flow Relationships and Aortic Root Phonocardiography in Normal Humans**

Because no intracardiac sound was recorded in the study from which Figure 1 was derived (17), another example will be used where simultaneous phonocardiography was obtained. In Figure 2, micromanometrically measured LV and aortic pressures, along with aortic root flow velocity, were recorded in another patient with normal LV and aortic valve function. A single cardiac cycle is demonstrated during rest (left panel), supine bicycle exercise (middle panel) and isoproterenol infusion (right panel). As in Figure 1, a pressure difference signal, here labeled the impulse gradient (18,19), is derived electronically and displayed at a scale that is 10 times the sensitivity of the LV and aortic pressures. Once again, a very early systolic gradient develops in an explosive fashion and is coincident with the maximum rate of change of aortic flow velocity (acceleration), well before the peak flow velocity. As inotropic stimulation increases, flow acceleration increases, associated with an increase in the peak impulse gradient and the peak flow velocity. Peak instantaneous transaortic pressure gradients as high as 35 mm Hg were reported in this study (19).

A simultaneous intraaortic phonocardiographic signal, derived from the aortic micromanometer, demonstrates sound frequencies that have a diamond shape, with correspondingly greater magnitudes as the inotropic state increases. The most important observation is that the sound energy peaks simultaneously with the flow velocity signal, as opposed to the pressure gradient signal.

This principle is reinforced in Figure 3, where pressure, flow velocity and impulse gradient signals are demonstrated in a normal sinus beat and a post-PVC beat in another patient without any evidence of LV or aortic valve disease. A more complete study of “innocent murmurs” was conducted by Stein and Sabbah (20), who pointed out that sound energy levels in the aortic root are of considerably greater magnitude than in the pulmonary artery. Their study cast doubt on the previously held notion that most innocent murmurs heard were from the pulmonary artery, because of its proximity to the chest wall.

**Mechanisms for Murmur Generation**

If velocity—and not pressure gradient—is associated more with the generation of cardiovascular sound, what other conditions or parameters must be considered to distinguish relatively “silent” blood flow from those conditions where murmurs occur in the absence of clinical pathology (innocent murmur)? Are increased flow velocity levels alone capable of generating mechanical energy (pressure) in the sound frequency range?

We now know that the generation of sufficient mechanical energy in the frequency range of cardiovascular sound, and of a magnitude high enough to be transmitted to the chest wall, is dependent on the presence of turbulent blood flow (21–23). In fluid flow through tubes, the factors that determine whether flow is “streamlined” or “turbulent” are described by a dimensionless number known as the Reynolds number (24–27):

$$Re = \frac{v \times D}{\eta}$$
The patients in the study of Spooner et al. (15) had decreased intraventricular velocities, a fact that falls below the range of values given in the study of Stein and Sabbah (22). Conversely, in those patients with increased intraventricular velocities, the average LV dimensions, presumably on the basis of LVH, the LV flow velocities appear to have been high enough, based on the principle of the Reynolds number, to generate turbulent blood flow.

### Left Ventricular–Aortic Systolic Pressure-Flow Relationships in Aortic Stenosis

The above examples demonstrate that cardiovascular sound energy can be generated in the presence of normal "physiologic" pressure gradients; that both the configuration and the timing of the sound energy envelope are more directly correlated to blood flow velocity waveforms than to pressure gradients; and that blood flow velocity, through the principle of the Reynolds number, can generate turbulent flow in individuals without the more commonly "recognized" valvular or vascular causes of murmurs.

In contrast, the most common pathologic cause of a systolic ejection murmur in societies with developed health care systems is aortic stenosis. Differentiation of a hemodynamically insignificant ejection murmur from aortic stenosis is the issue that most often concerns the clinician at the bedside (4,8,30,31). To evaluate and compare the pressure-flow relationships and the concept of the Reynolds number in this disease process, an example of critical aortic stenosis is illustrated in Figure 4.

Micromanometer-derived LV and aortic pressures are shown with a LVOT flow velocity signal derived from a catheter-mounted electromagnetic probe. An intraaortic cardiovascular sound recording demonstrates the classic diamond-shaped ejection murmur. Note that the peak flow velocity is in midsystole, which again coincides with the peak of the systolic murmur. Because the convective acceleration component (the second term of equation 1) now dominates,

### Table 1. Calculation of Reynolds Number for Patients in the Study by Spooner et al. (15)

<table>
<thead>
<tr>
<th>Increased Intraventricular Velocities</th>
<th>Average Peak Velocity (cm/sec)</th>
<th>Average LV Systolic Dimension (cm)</th>
<th>Calculated Reynolds Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not present</td>
<td>&lt; 70</td>
<td>3.81</td>
<td>&lt; 5005</td>
</tr>
<tr>
<td>Present</td>
<td>145</td>
<td>2.90</td>
<td>7891</td>
</tr>
</tbody>
</table>

where \( \rho \) = fluid density, \( \eta \) = fluid viscosity, \( \nabla \) = the mean linear (average) flow velocity and \( D \) = the tube diameter. This number is actually the ratio of local and convective acceleration forces (equation 1) to viscous forces (those secondary to viscosity of the fluid and shear forces developed along the walls of the tube) (25,27). The principle was first applied to study of the human circulation by McKusick (28) and later by Rushmer and Morgan (29). Although the concept originally evolved from models of steady (nonpulsatile) flow in a long, straight tube far from a flow inlet, the Reynolds number has been applied to many variations of this model and appears to be quite useful. Turbulence only occurs after the Reynolds number increases to a critical value that can be achieved by varying any of the components of equation 2. During any particular physical examination, one could assume that the individual patient’s blood density, viscosity and cardiac geometry (except for HCM) would be relatively constant, leaving the Reynolds number to be determined primarily by variations in blood flow velocity. This conceptually fits with the observations shown in Figures 2 and 3. It should also be noted that, from one subject to another, the Reynolds number would predict that the same blood flow velocity might generate turbulent flow in one, but not the other, depending on associated cardiovascular geometry.

Using a catheter with a hot film anemometer probe, Stein and Sabbah (22) measured point velocities in the aortic root and demonstrated that turbulence occurs in the normal human aortic root when Reynolds numbers are in the range of 5,700 to 10,000. To estimate what order of magnitude Reynolds numbers might have been present in the study of Spooner et al. (15), the average values of LV velocities and LVOT dimensions provided in their study were used to calculate Reynolds numbers, as shown in Table 1.

Of interest, the average Reynolds number for the group of patients without increased intraventricular velocities in the study of Spooner et al. (15) is estimated to be <5,000, which falls below the range of values given in the study of Stein and Sabbah (22). Conversely, in those patients with increased intraventricular velocities and systolic murmurs, the average Reynolds number is estimated to exceed 7,890, remarkably close to the average value of 7,060 found in the seven “normal” patients with flow turbulence in the study of Stein and Sabbah (22). Note that these values were obtained despite the fact that the LV dimensions in the group of patients with increased intraventricular velocities and systolic murmurs were less than those without increased intraventricular velocities, a fact that would tend to decrease the Reynolds number. Thus, although the patients in the study of Spooner et al. (15) had decreased LV dimensions, presumably on the basis of LVH, the LV flow velocities appear to have been high enough, based on the principle of the Reynolds number, to generate turbulent blood flow.
the local acceleration component contributes very little to the overall gradient between the LV and the AO. Thus, the gradient is more directly related to the second power of blood flow \( Q^2 \) and, in contrast to the examples where the local inertial component was dominant, its peak magnitude now occurs coincident with the peak magnitude of blood flow. This observation has often led clinicians to believe that the gradient itself is the cause of the murmur. However, the Reynolds number concept demonstrates again that it is turbulent blood flow that is the cause of the systolic murmur in aortic stenosis.

In the form given in equation 2, the Reynolds number concept becomes less intuitive when applied to aortic stenosis because the geometric factor “D” appears in the numerator, and would lead one to believe that turbulence would be lessened as the LVOT and aortic valve area decreased. The problem is clarified if one remembers that the term \( \bar{V} \) in equation 2, represents mean linear, or average velocity, across the flow field. Where the flow velocity spatial profile is relatively flat, as occurs in the ascending aortic root in normal conditions, the use of “sample” velocity measurements, such as those made in Figures 1 to 3, or in the studies of Stein and Sabbah (22,23), may be acceptable. However, in conditions where small orifice flow and jet formation conditions exist such as in aortic stenosis, the Reynolds number concept is more easily understood if one uses volumetric flow rate (cc/sec) instead of velocity (cm/sec) (25,28). Volumetric flow \( Q \) is related to average velocity by the relationship:

\[
Q = \pi r^2 \bar{V} = \frac{\pi D^2}{4} \dot{V} \text{ or }
\]

\[
\dot{V} = \frac{4}{\pi} \frac{Q}{D^3}
\]

where the symbols are as defined in equations 1 and 2. Substituting equation 4 into equation 2 yields:

\[
Re = \frac{4\rho}{\pi \eta} \times \frac{Q}{D}
\]

This form of the Reynolds number equation now predicts that turbulence may be dependent on increases of \( Q \) such as with exercise or other inotropic stimulation, decreases in effective cross-sectional area (D) as in aortic stenosis, or with decreases in blood viscosity \( \eta \), as in anemia. Expressed this way, the formula is more intuitive and helps to explain the decrease in intensity, or even absence of the murmur in aortic stenosis when severe LV dysfunction is present (blood velocity may still be much higher than normal in aortic stenosis in the presence of a low ejection fraction, but the actual flow rate, in cc/sec, may be below normal). When considered from an advanced fluid dynamics standpoint (25–27), these simplified mathematical approaches are limited, but were used here so that clinicians might more easily understand the principles involved.* Of ancillary interest is the fact that the slow rising “Parvus et Tardus” nature of the aortic pressure waveform is not mimicked by the LV outflow ejection waveform. The cause of the delayed upstroke of the aortic pressure waveform is often misunderstood, with some believing that it is a result of delayed and prolonged ejection secondary to a fixed LV outflow obstruction. Indeed, the marked differences in the waveform characteristics of the ascending aortic root pressure pulse, compared to its corresponding volumetric flow, is secondary to Bernoulli pressure losses where potential energy (pressure) is converted into kinetic energy (velocity). These losses may be substantial in the central flow jet itself and may account for discrepancies in echocardiographic-Doppler estimated pressures and actual catheter measured pressures in aortic stenosis. In a recent study, Cape et al. (34) used a Reynolds-number-based approach to reconcile these differences.

---

Of interest, even the FDA requires the measurement of the Reynolds number to quantify the level of turbulence in the aortic root when testing prosthetic aortic valves (35,36).
Left Ventricular–Aortic Systolic Pressure-Flow Relationships in HCM: Evidence of Complex Multisite Generation of Systolic Murmurs

In addition to the hemodynamic and geometric factors considered previously, the origin of systolic ejection murmurs detected on the chest wall may not be the result of a single source of turbulent flow. Because the patients described in the study of Spooner et al. (15) had some characteristics similar to those found in patients with HCM (37–41), an example of the complexity of the origin of systolic murmurs in that disease entity is illustrated in Figure 5.

In this case, transeptal and retrograde cardiac catheterization, using catheters with multiple micromanometers, allowed for the recording of left atrial (LA), LV, LVOT, and aortic pressures. Three intracardiac/vascular phonocardiograms are displayed, along with an external phonocardiogram obtained by placement of a microphone on the patient’s chest wall. A normal sinus beat, a premature ventricular contraction and a postcompensatory pause sinus beat are shown. The vertical line represents the point in time at which the anterior leaflet of the mitral valve abuts against the septum, labeled as SAM-septal contact (SSC), and obtained by simultaneous M-mode echocardiogram, but not shown here (42).

An early systolic diamond-shaped murmur occurs in the aortic root. This corresponds in timing with the compression of volumetric LV and aortic ejection into early systole (42–46). In the LVOT, sound energy vibrations are more diffusely distributed both before and after SSC, but with increased intensity in early systole, also consistent with the knowledge that the majority of volumetric flow occurs in the first half of systole (42–46), but that high velocity (albeit low volume outflow) occurs in late systole (47). Following SSC, we see a burst of energy in the LA phonocardiogram, no doubt caused by late systolic mitral regurgitation (38–40). The external phonocardiogram suggests a composite of these various intracardiac and intraaortic sources of sound energy. During the postectopic ventricular beat, all of these signals are accentuated in intensity, although with slightly different timing, as SSC occurs earlier in systole.

As in aortic stenosis, the application of the Reynolds concept to HCM is more easily understood if one uses volumetric flow (Q), instead of average velocity (V), as given by equation 5. In early systole, the vast majority of LV emptying occurs in the first half of systole (42–46). As a result, the “Q” term dominates the development of turbulence and cardiovascular sound. In late systole, very little in the way of LV emptying occurs, as the end-systolic volume of the LV has achieved near minimal size by midsystole (42–46). However, the LVOT, via SSC, as well as the entire ventricle, via cavity obliteration, now achieves very small values of “D,” allowing for continued sound generation in the outflow tract as shown in the LVOT phonocardiographic signal in Figure 5. The principles highlighted earlier can also explain the generation of systolic turbulence in the left atrium. The coexisting mitral regurgitation murmur, which appears in mid- to late systole after SSC, must also represent a low volume flow rate, albeit high velocity mitral regurgitant jet. Here, the “D” term of equation 5 dominates, as the mitral valve is primarily closed, although not totally competent.

Is it possible that some of the patients with hypertensive hypertrophic cardiac disease reported in the study by Spooner et al. (15) had systolic murmurs that resulted from a similar composite of several acoustic energy sources within the hypertrophic hypertensive heart? The subset of patients that fell into the authors’ intermediate and indeterminate groups certainly had a combination of increased intraventricular velocities and mitral regurgitation demonstrated by echocardiographic-Doppler techniques. Some murmurs described in their study were subjectively reported (although not recorded) as mid- to late systolic, and they responded to maneuvers in a manner similar to patients with HCM. Only further analysis, with more sophisticated techniques, would lend evidence to such a hypothesis.

Conclusions. The data presented in the study of Spooner et al. (15) may not directly support the conclusion that increased intraventricular velocities are responsible for generating the systolic murmurs reported, but extrapolation from what we have learned from invasive studies in the past, and the values of the Reynolds numbers calculated from their data in this review, would support a cause-and-effect relationship. Although the authors believe that their select population of patients may have led to an overestimation of the prevalence of such murmurs, it is also possible that this study actually underestimates the degree to which hypertensive heart disease is responsible for the generation of systolic ejection murmurs as, in their intermediate and indeterminate groups, the LV outflow dynamics may well have been more dominant than any coexistent mild mitral or tricuspid regurgitation. Overall, their study highlights some important clinical observations in this era of high prevalence of hypertension, significant morbidity of hypertensive hypertrophic heart disease and decreased experience and expertise of physicians in cardiac auscultation.

To interpret their results better, the basic characteristics of pulsatile pressure and flow ejection dynamics were presented, primarily to illustrate the relationship of blood flow rates, and not pressure gradients, to the generation of cardiovascular sound. The principle of the Reynolds number was reviewed, in which blood flow rates play a major role in the production of turbulent flow, a necessary prerequisite for the production of cardiovascular sound. Finally, an example of a patient with classic hypertrophic cardiomyopathy was presented, to demonstrate the fact that systolic murmurs heard on the chest wall can be the result of a composite of multiple sources of intracardiac and intravascular turbulence and sound energy.

I thank Maj. Terry Bauch, MC, of the Cardiology Service, Department of Medicine, and the Medical Photography Department, Brooke Army Medical Center, Fort Sam, Houston, Texas, for assistance. Deep gratitude is offered for the support and help of many technicians, medical editors, fellows, colleagues, mentors and department chairmen at Brooke Army Medical Center, with whom...
I was fortunate to work during the years between 1969 and 1986. In particular, I would like to dedicate this review to the late Col. George M. McGranahan, MC, U.S. Army Ret., former Chief of Cardiology and Director of Professional Services at Brooke Army Medical Center, without whose support the studies that generated the observations included here would not have been possible.

References