Development in the 1950s of the transseptal technique for left heart catheterization is described. Initial studies in animals and human cadavers were followed up by left atrial puncture with measurements of left atrial and left ventricular (LV) pressure (the latter using a small plastic catheter) in patients with cardiac disease. Many such procedures were performed safely without complications. Subsequent modification of the original technique for percutaneous catheter insertion allowed placement of a larger taper-tipped catheter in the LV chamber for selective LV angiography. Early clinical research studies at the National Heart Institute were performed using the transseptal method; these included investigation of the effects of increasing afterload on the normal and failing left ventricle by means of a graded angiotensin infusion to induce a progressive increase in aortic pressure. A marked decrease in the stroke volume occurred with increased afterload in the failing heart. This finding later led to the concept of afterload mismatch with limited pre-load reserve. Another early transseptal catheterization study in which measurements of LV pressure were made at different locations within the left ventricle as well as in the left atrium confirmed the presence of cavity obliteration in some patients and true obstruction in the LV outflow tract in many others. In addition, left ventriculography showed that obstruction was caused by abnormal anterior position during systole of the anterior mitral valve leaflet. With growing acceptance of retrograde catheterization of the left ventricle, the use of the transseptal technique for diagnostic purposes declined. However, in recent years, substantial renewed application of the transseptal method has occurred for special diagnostic and therapeutic purposes, including balloon valvuloplasties and electrophysiologic ablation procedures within the left heart. (J Am Coll Cardiol 2008;51:2107–15) © 2008 by the American College of Cardiology Foundation

The late 1940s and early 1950s encompassed a burgeoning era in the cardiovascular field. It featured Blalock and Taussig implementing palliative surgery for tetralogy of Fallot, Crafoord and Gross treating coarctation of the aorta surgically, and application of right heart catheterization for the diagnosis of acquired and congenital heart disease as reviewed by Cournand et al. (1). In mid 1956, 2 of a group of interns in surgery at the Johns Hopkins Hospital were sent by famed surgeon Alfred Blalock to the then National Heart Institute in Bethesda, Maryland, for a period of research training in the Clinic of Surgery headed by Andrew Morrow. At that time catheterization of the left side of the heart was still a relatively novel procedure, but soon after reaching the National Institutes of Health (NIH) Clinical Center, as one of those two interns, I saw demonstrations of several methods then in use (2). Among these were the suprasternal approach (a long needle passed retrosternally through the great vessels and into the left atrium [LA]), the posterior transthoracic method (a needle passed lateral to the vertebral column into the LA), the transbronchial approach to the LA (used by Dr. Morrow), and direct puncture of the left ventricle by the subxyphoid or apical approaches (2). I was privileged to assist Dr. Morrow in a number of procedures as he anesthetized the trachea by direct needle injection of anesthetic into the larynx in patients about to undergo the transbronchial procedure. A long needle was then passed through the bronchoscope to a site in the left main stem bronchus just beyond its origin, where the puncture was made into the LA (which is in contact with the bronchus at that location). I would then pass a long, small plastic catheter to him and he, in turn, would insert it through the needle to enter the LA and frequently further into the left ventricle (2). Needless to say, none of these procedures for left heart catheterization was particularly comfortable for the patient and, with the exception of the transbronchial method, they carried considerable risk. I thought at the time, there must be a better way, and what follows is an account of my research trajectory with a novel technique.

Early Work on the Transseptal Method

It was customary for the trainees at the NIH to carry out diagnostic right heart catheterizations. Fluoroscopy was performed after dark adaptation with red goggles, because at
that time image intensification radiographic equipment was not available; consequently, the X-ray exposure was high and exposure was time limited. One of the techniques then in use at the NIH in patients having an atrial septal defect was to pass balloons of several sizes attached to catheters through the septal defect to assess its size. When a catheter is passed upward from the saphenous vein of the leg into the right atrium, it is quite easy to enter the LA through the interatrial defect and to manipulate the catheter into the pulmonary veins and the left ventricle. In 1957, a visitor observing me performing such a procedure wondered whether it might be possible to enter the LA if the septum were intact; I replied that perhaps it might be accomplished with a special needle. Shortly thereafter I began work with the goal of designing and constructing, for experimental use in animals, a long needle having a curved end distally and an arrow-shaped handle at the proximal hub end to permit controlled rotation of the curved needle tip. Such a needle was then constructed for me by the machine shop at the NIH, the needle being 15 mm longer than the Courand catheter through which it was passed. Some months later a longer 17-gauge version through which a PE50 polyethylene catheter could be passed was produced for human use by the Becton-Dickinson Company (Fig. 1). (In those days, I had not given a thought to applying for a patent).

Experiments proved successful and safe in the dog, and the puncture site in the atrial septum was shown to heal. These experiments showed successful measurements of left atrial and left ventricular (LV) pressures (the latter obtained with the small plastic catheter), and left heart angiograms with left atrial injection could also be obtained (Fig. 2). This work was presented at a surgical meeting in 1958 and published in 1959 (3).

After completing the experimental studies, using the longer transseptal needle, I then carried out experiments in cadavers after post-mortem examinations by the NIH pathologist to directly visualize the transseptal puncture site with the right atrium opened widely by an incision. A catheter was passed through the right saphenous vein into the right atrium, followed by the transseptal needle, which was allowed to rotate freely as it was advanced, and the catheter tip containing the withdrawn needle was then rotated postero-medially and positioned at the upper margin of the fossa ovalis. The needle was then pushed forward to achieve septal puncture, and under these conditions the LA was almost always readily entered. In some of the cadavers, the right atrium was enlarged, but a successful puncture remained relatively easy to accomplish.

Initial Catheterizations in Patients

Clinical application then followed, in collaboration with Drs. Andrew Morrow and Eugene Braunwald. The first patient was a young man under consideration for surgery for mitral regurgitation who agreed to be the first subject for the new procedure. The first puncture attempt was successful, and severe mitral regurgitation was evidenced by giant V waves on the left atrial pressure tracing (Fig. 3) (4). There were no complications in the initial series of 13 patients, all of whom had mitral valve disease with left atrial enlargement; the bulge of the LA into the right atrium could be appreciated during manipulation and positioning of the catheter and needle (4). A second series of 130 patients was published in 1960, in which left atrial and LV pressures were measured in many patients using the PE50 catheter (Fig. 4), and again no complications occurred (5). Application of the transseptal method in the pediatric age group also was described (6).

That year (1960) I decided to leave Bethesda for residency training in New York, where I performed demonstrations of the transseptal technique in a few cardiac catheterization laboratories.

Later Modifications of the Transseptal Method

In the late 1950s and early 1960s the development of heart lung machines began to allow open surgical repair of
selected mitral and aortic valve disorders, as well as congenital heart defects. These advances required assessment of the severity and type of mitral and aortic valve lesions, visualization of congenital anomalies, and quantitative analysis of LV function. In that pre-echocardiography era, these goals could be accomplished by placing a large catheter in the left ventricle by the transseptal route for performing selective left ventriculography. Shortly before my departure for New York, Dr. Edwin Brockenbrough, a young clinical associate in the Clinic of Surgery at the NIH, showed me a transseptal needle that he had instructed the NIH shop to modify by adding a smaller 21-gauge needle to the tip of the transseptal needle. A tapered tip catheter replaced the Cournand catheter, which would allow application of the

**Figure 2** Left Atrial Injection of Contrast Medium Via the Transseptal Needle

Angiogram of the normal canine left heart shows left atrium (top), left ventricular diastole (center) and systole (bottom). Reprinted with permission from Ross (3).

**Figure 3** Transseptal Needle Puncture of the LA in the First Patient

Pressure tracing shows severe mitral regurgitation evidenced by giant V waves on the left atrial pressure tracing; pressure was also recorded as the needle was withdrawn from the left atrium (LA) across the interatrial septum into the right atrium (RA), where the pressure was normal. Reprinted with permission from Ross et al. (4).

**Figure 4** Pullback Tracing From LV to LA Obtained With the Small Plastic Catheter

The patient had mitral stenosis with atrial fibrillation, and the left atrial (LA) tracing shows a pattern typical of mitral stenosis, with a delayed downslope of the V-wave and a large pressure gradient across the mitral valve. Reprinted with permission from Ross et al. (5). LV = left ventricle.
percutaneous Seldinger approach (7) using a guidewire for entering the right femoral vein. Once the needle tip was properly positioned against the fossa ovalis and the puncture made with the 21-gauge needle, the catheter and the needle would be advanced together into the LA. The needle would then be withdrawn to the site of the puncture and the catheter alone advanced into the left ventricle. I agreed with this plan, and later in 1960 he and Braunwald published the experience with this approach (8).

While I was in New York, Eugene Braunwald was appointed head of the new Cardiology Branch of the National Heart Institute and in 1962, my residencies completed, I accepted his invitation to become head of the Section on Cardiovascular Diagnosis of the Cardiology Branch at the NIH. That year, experience with the first 450 transseptal catheterizations performed at the Clinical Center of the NIH, including those performed with the modified approach, was published in which there was no mortality and few complications (9). The equipment used in the modified approach was also detailed (Fig. 5) (9). Four years later, in 1966, my experience with the modified transseptal method with some additional modifications was described in 350 additional patients, and experiences reported from other institutions were reviewed (10). The only complication in this series was 1 nonlethal aortic puncture. Recommendations included the use of radiographic landmarks for the site of left atrial puncture in the presence of a normal or greatly enlarged left atrial chamber. Relative contraindications to transseptal left heart catheterization were proposed including giant right atrium, severe rotational abnormalities of the heart and great vessels, kyphoscoliosis, marked dilation of the ascending aorta, anticoagulation therapy, and evidence of left atrial thrombus or a recent history of systemic embolization (10).

Some Early Research Applications of Transseptal Left Heart Catheterization

Transseptal left heart catheterization had become a standard diagnostic procedure in the 2 NIH catheterization laboratories in the 1960s, and some investigations concerning the left ventricle were added to the diagnostic catheterization in selected patients.

Studies on LV Function

Heart failure. In the experimental laboratories at the NIH, after the pioneering work of Abbott and Mommaerts in isolated cardiac muscle (11), Ed Sonnenblick began his studies in the early 1960s on length–tension and force–velocity relations in isolated cardiac muscle (12). These studies stimulated my own interest in studying these phenomena in the intact heart, particularly the influence of afterload, pre-load, altered inotropic state, and heart rate on LV performance. At the same time, a number of clinical and laboratory studies on heart failure were ongoing within the Cardiology Branch at the NIH (13).

An attractive target for clinical study was to compare the effects of changing the afterload in the normal and failing heart. Angiotensin II seemed to be suitable as a vasopressor agent for this purpose because it is short-acting and has little direct inotropic and chronotropic actions. Accordingly, we studied 18 patients with a variety of cardiac disorders who were undergoing diagnostic cardiac catheterization (14). The patients had mild mitral stenosis without regurgitation, mild pulmonic stenosis, a functional heart murmur or heart failure with dyspnea on exertion and cardiomegaly on chest radiograph. Graded doses of angiotensin were administered to achieve similar increases in LV systolic pressure in all patients (14). In most patients ventricular function, expressed as the relation between LV end-diastolic pressure and the LV stroke work index, increased during the angiotensin infusions, (group 1) (Fig. 6, upper panel), accompanied by an increase in the stroke volume index (group 1) (Fig. 6, lower panel). In other patients, the stroke work index increased only slightly (group 2) (Fig. 6, upper panel), and the stroke volume increase was mild or absent (group 2).
However, in the remaining patients, the ventricular function relations were flat (group 3) (Fig. 6, lower panel), and in this group the stroke volume index decreased markedly (group 3) (Fig. 6, lower panel). The increases in LV systolic pressure were closely similar in all 3 groups (Fig. 6, lower panel) (14). The patients in group 3 had either cardiomegaly, a history of myocarditis, or familial cardiomyopathy, and all but 1 had orthopnea and limited activity. This study first showed the enhanced sensitivity of the failing human left ventricle to increased afterload.

In subsequent laboratory studies in animal hearts, the pre-load, inotropic state, and heart rate were held constant, while changes in afterload alone were induced. This was accomplished by altering aortic pressure from a pressure reservoir during a single diastolic interval (afterload being determined by the LV systolic pressure, and also defined as systolic wall force or tension) (15). These sudden changes in afterload alone allowed demonstration in the normal heart of the striking effect of increasing the afterload to decrease the stroke volume, and vice versa. Also, the inverse relation between afterload and the velocity of LV wall shortening (the force–velocity relation) was shown, the entire relation being shifted upward by beta-adrenergic stimulation (15) and downward by depressed myocardial contractility (16). Other experimental studies in the normal heart confirmed the inverse relation between afterload and the stroke volume when the pre-load was fixed (Fig. 7); when the pre-load was allowed to vary, the stroke volume could be maintained as the afterload was increased while the pre-load increase compensated for the augmented afterload (Fig. 7) (17). The afterload in this acute study was represented by the systolic LV pressure. When the limit of pre-load reserve was reached by volume loading to a very high ventricular filling pressure, even in the normal heart further increases in afterload result in a decrease in the stroke volume (Fig. 7) (17).

These initial clinical and laboratory observations led to the concept of “afterload mismatch with limited pre-load reserve” (18), afterload mismatch indicating inability of a ventricle to maintain the stroke volume or wall shortening at the prevailing level of systolic arterial pressure. In severe heart failure, when the cardiac output is reduced it can be considered that afterload mismatch exists under resting conditions.
conditions, because chamber dilation and relative wall thinning cause increased LV wall stress even at a normal systolic pressure (18), hence the effectiveness of pharmacological reduction of the afterload with vasodilators to improve the cardiac output in this setting.

The effects on the failing left ventricle of increasing the afterload during angiotensin infusion (15) can be readily understood using the wall stress–volume diagram. In the setting of heart failure, the striking decrease in the stroke volume associated with an increase in afterload is caused by 2 factors: the absence of pre-load reserve and enhanced sensitivity of the failing ventricle to increased afterload. This enhanced sensitivity is the result of decreased myocardial contractility, reflected in the reduced slope of the end-systolic wall stress–volume relation (Fig. 8). The actions of a vasodilator on the failing heart also can be appreciated using this diagram (Fig. 8).

Valvular heart disease. The framework of afterload mismatch and limited pre-load reserve has also proved useful in explaining some phenomena in valvular heart disease (19). For example, in aortic stenosis when the ejection fraction (EF) begins to decrease, the pre-load reserve of the left ventricle is often limited by cardiac hypertrophy and increased myocardial stiffness. As the valve narrowing progresses, the LV afterload increases further, and the LV EF can become markedly reduced, primarily because of afterload mismatch without pre-load reserve (Fig. 9). In this setting the EF often can be substantially restored (in this example from 33% to 52%) by reducing the afterload with replacement of the aortic valve (Fig. 9) (19). Of course, such a dramatic favorable effect can occur only if pre-operative myocardial degeneration is not too severe.

Another example of afterload mismatch can sometimes occur in the setting of severe mitral regurgitation associated with significantly impaired LV function. After mitral valve replacement, the opposite effect to that described above after aortic valve replacement can be seen. Pre-operatively, the LV EF may be only mildly reduced and the stroke volume increased because of the large low-impedance leak into the LA (Fig. 10). However, when the mitral valve is replaced, the depressed left ventricle must then eject the entire stroke volume into the high impedance of the aorta, and the EF becomes substantially reduced (Fig. 10) (19). With widespread appreciation of the criteria for and proper timing of mitral valve replacement in this condition, such events have become infrequent.

Thus, what began as an early clinical investigation using transseptal left heart catheterization to study the effect of induced increases in afterload on LV function (14) led to observations that influenced understanding of normal heart function.

Figure 7 LV Pressure-Volume Diagrams in the Normal Heart
In the baseline pressure-volume loop (1), the stroke volume (SV) is indicated, and the arrow indicates the ejection portion of the loop. With initial induced elevation of left ventricular (LV) systolic pressure, the stroke volume decreases (loop 2), but it is restored by increased diastolic filling (loop 3). When the systolic pressure is increased after marked volume loading, the limit of pre-load reserve is reached at LV end-diastole, afterload mismatch occurs, and the stroke volume decreases (loop 4). Reprinted with permission from Ross (19).

Figure 8 LV Wall Stress–Volume Diagrams in Heart Failure
The normal end-systolic wall stress–volume relation is represented by the dashed line, and this relation in heart failure is shifted downward with reduced slope. The resting left ventricular (LV) wall stress–volume loop in heart failure (1) shows little pre-load reserve, and increased afterload induced by angiotensin (loop 2) causes a marked decrease in the stroke volume (SV2). Administration of a vasodilator (loop 3) compared with loop 1 causes reduced afterload particularly early and late during LV ejection, an increase in stroke volume (SV3), with a modest decrease in LV end-diastolic volume. Reproduced with permission from Ross J Jr. Mechanisms of cardiac contraction: what roles for preload, afterload and inotropic state in heart failure? Eur Heart J 1983;4:19–38.
function, as well as abnormal cardiac function in clinical settings of altered afterload.

The Riddle of Obstruction in Hypertrophic Cardiomyopathy (HCM)

In the early 1960s, a controversy raged in the cardiology community over whether the elevated LV systolic pressure, compared with that in the aorta, observed in many patients with HCM (then often called idiopathic hypertrophic subaortic stenosis) was caused by true intraventricular obstruction to ventricular ejection, or to an artifact without obstruction consequent to catheter trapping with cavity obliteration during systole in the markedly hypertrophied left ventricle. The latter phenomenon, supported particularly by Criley et al. (20) as well by earlier studies (21), clearly occurs in some patients. However Wigle et al. (22), and the group at the NIH, which included Morrow (who had developed a surgical procedure for this condition, septal myomectomy), Braunwald, and others, believed there to be true obstruction in the LV outflow tract in many patients (23). The controversy reached a point at which Dr. Morrow invited Dr. Criley and myself into the operating room to observe his surgical procedure. During the course of the operation (before myomectomy), each of us was instructed to place an index figure through the incision in the aorta, down through the aortic valve into the LV chamber of the still beating heart. Dr. Criley described squeezing distally but none proximally, whereas I felt more squeezing in the septal area than distally (observations which just happened to be consonant with our biases!). So, of course, nothing was settled. This patient, like many others undergoing this surgical procedure, had near abolition of the elevated LV systolic pressure at post-operative cardiac catheterization and became nearly asymptomatic.

It seemed that transseptal catheterization offered a potential approach to prove or disprove the presence of true obstruction. In a series of patients being considered for surgical treatment based on clinical findings (which included, among many other features, the presence of a murmur and localized thrill, and enhanced murmur with a Valsalva maneuver [23]), the pre-operative evaluation included transseptal left heart catheterization (24). During the catheterization, care was taken to record the pressure in the LA just in front of the mitral valve and also to record the pressure immediately after traversing the mitral valve in the LV inflow tract (the catheter position documented by fluoroscopy and in some patients by LV angiography). The catheter was then advanced further into the LV apex. Next, it was slowly withdrawn through the left ventricle back
across the mitral valve. Aortic pressure was measured separately. Two patterns of pressure change were evident during this maneuver (Fig. 11). In one type, with the catheter in the LV apex, the systolic pressure exceeded aortic pressure, but became normal in the inflow tract of the left ventricle where it equaled aortic systolic pressure, a pattern consistent with cavity obliteration and catheter trapping (Fig. 11, left diagram). In the other type, observed in most of these selected patients, the LV systolic pressure was elevated in both the apex and the inflow tract of the left ventricle as the catheter was withdrawn, indicating obstruction above the inflow tract, that is, in the outflow tract (Fig. 11, right diagram) (24). That the pattern of pressure change shown in the right panel of Figure 11 indicated true obstruction was further supported by intraoperative studies using a flowmeter to show that most of the stroke volume was delivered during the period of the pressure gradient (24).

The presence of obstruction was further established by selective left ventriculography. In these studies, the mechanism of the obstruction was shown to be caused by abnormal apposition of the anterior mitral valve leaflet against the hypertrophied septum during LV systole (Fig. 12) (24,25). Several years later when echocardiography had come into wide use, this phenomenon was described as systolic anterior motion of the mitral valve in patients with obstructive HCM (26). Although not pathognomonic of HCM, this echocardiographic sign is now generally considered to reflect obstruction at rest, or during a Valsalva or other maneuver used to induce obstruction.

Septal myomectomy has been performed in many centers around the world for treating obstructive HCM, generally with good results (27), and more recently alcohol ablation of septal myocardium delivered by injection through the septal coronary artery has found increasing application (28).

**Decline and Resurgence of the Transseptal Method**

Late in the 1960s and in the early 1970s, selective coronary angiography was being developed and applied, initially by Sones and Shirey (29) and somewhat later by Judkins (30), who used the percutaneous femoral approach. The ease and safety with which the special catheters being used for coronary angiography could be passed retrograde across the aortic valve into the left ventricle was recognized. This led to increasing use of the retrograde catheterization method for obtaining LV pressures and angiography, with a corre-
sponding decrease in use of the transseptal method for diagnostic purposes. However, as my own clinical and laboratory research interests shifted to myocardial ischemia and infarction, and later to molecular cardiology (31), it has been gratifying for me to observe renewed use of transseptal catheterization for specialized diagnostic and therapeutic procedures. These initially involved its widespread application for performing balloon valvuloplasties, particularly of the mitral valve. More recently the transseptal method is being used frequently for left-sided catheter placements by clinical electrophysiologists carrying out diagnostic and ablation procedures. These and other applications of the transseptal method, such as with temporary LV (32) assist devices, are described in detail by Babaliaros et al. in the accompanying article.

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