Novel Approaches to Cardiac Valve Repair
From Structure to Function: Part II
Magdi H. Yacoub, FRS; Lawrence H. Cohn, MD

In Part I of this article, several aspects of valve structure and function and their possible clinical relevance were discussed. We now review the clinical evolution and application for various forms of valve repair and outline some of the factors relating to the timing and choice of particular types of repair or replacement and, whenever appropriate, repair versus replacement. In addition, future prospects of valve repair based on understanding of the sophisticated function and structure of valves and the possible future contribution of tissue engineering are discussed.

Valve Repair: Evolution of a Concept
The very first attempts at surgical treatment of heart valve disease were directed toward repair of mitral stenosis in the early 1920s by Elliot Carr Cutler in Boston and Sir Henry Souttar in London. Although some of these operations were successful, it was approximately 30 years before mitral valvotomy was established by Bailey in the United States and Lord Brock and O.S. Tubbs in the United Kingdom. The next heart valve operation to be attempted was repair of mitral regurgitation by Lillehei et al, who in 1957 reported “surgical correction of pure mitral regurgitation by annuloplasty under direct vision.” Shortly after that, Dwight McGoon, at the Mayo Clinic, introduced “repair of mitral regurgitation for ruptured chordae tendineae by triangular resection of the prolapsing segment,” a major contribution. With the introduction of mechanical valve replacement by Harken, Starr, and others and biological valves (homografts) by Donald Ross and Brian Barratt-Boyes in the early 1960s, there was a swing toward valve replacement. More recently, however, there has been a gradual realization that the ideal operation may be a restorative (repair) operation attempting to reproduce some of the sophisticated functions of a normal valve. This was accompanied by refining and evolving new techniques for repair of different valves by Carpentier and others. During the same period, valve substitutes have also been evolving, with improvement in design and flow characteristics and reduction of the rate of complications. However, some inherent problems, such as thrombogenicity of mechanical valves and degeneration of tissue valves, have not been eliminated. The availability of many options offers opportunities but also problems of choice.

Decision-Making in Valve Surgery
Optimal management of specific lesions in individual patients is critically dependent on appropriate decision-making with regard to the timing and type of operation, 2 issues that are closely related and interdependent. These decisions rely on defining the goals of valve surgery, which include symptomatic relief, restoration of both exercise capacity and quality of life, and, importantly, longevity compared with age-matched controls. The information needed to make these decisions is sometimes incomplete, and therefore, clinicians have to depend on predictions and possibly biases as well as the experience and skills available to the group. Some of these uncertainties are highlighted in the American Heart Association/American College of Cardiology guidelines for management of valve disease.

From Imperial College School of Medicine, Heart Science Centre, Harefield Research Foundation, Harefield, Middlesex, UK, and Brigham and Women’s Hospital, Harvard Medical School, Boston, Mass.

Correspondence to Magdi Yacoub, Heart Science Centre, Harefield Research Foundation, Harefield, Middlesex, UB9 6JH, UK. E-mail m.yacoub@imperial.ac.uk
(Circulation. 2004;109:1064-1072.)
© 2004 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org
DOI: 10.1161/01.CIR.0000115634.66549.4D
Patient- and Valve-Specific Information Required for Decision-Making About Timing and Type of Operation

- Symptoms
- Severity of valve disease
- Valve structure in relation to function
- Calcification
- Ventricular function
- Pulmonary vascular resistance
- Rate of progression
- Associated aortic disease
- Comorbid conditions

Prognostic indicators of survival and progression of valve disease

A. Biochemical, eg, lipids, homocysteine
B. Genetic

Application of reparative procedures to the aortic valve has lagged behind because of the apparently irreversible changes produced by cusp calcification, the common loss of substance and retraction of cusp tissue in aortic regurgitation, and the lack of durable biological material suitable for supplementing valve tissue. Nevertheless, several reparative techniques are being used successfully in specific types of aortic disease.

Aortic Valve Repair

Application of reparative procedures to the aortic valve has lagged behind because of the apparently irreversible changes produced by cusp calcification, the common loss of substance and retraction of cusp tissue in aortic regurgitation, and the lack of durable biological material suitable for supplementing valve tissue. Nevertheless, several reparative techniques are being used successfully in specific types of aortic disease.

Aortic Stenosis

In neonates, infants, and children, severe congenital aortic stenosis results in apparent disorganization of the valve with complete or partial absence of one or more of the commissures. Nevertheless, balloon valvuloplasty and/or open valvotomy or repair can provide excellent palliation. Open valvotomy or repair in these patients usually consists of transforming the valve to bicuspid configuration with sharp division of the appropriate commissure(s) and mobilization of the hinge mechanism. The mobility of the cusps can be enhanced by “shaving” the aortic surface of the commissural raphe and possibly by enlarging the noncoronary sinus of Valsalva with an autologous pericardial patch. This operation may allow children to grow normally to adolescence or early adulthood, when a more definitive approach, such as the Ross operation, may be applied. More radical approaches, such as the early application of the Ross procedure with or without Konno-Rastan repair, may be required in infancy but are largely unwarranted before the age of 15 years.

Aortic Regurgitation

Recent advances in understanding the different mechanisms of aortic regurgitation have resulted in the evolution and application of valve-conserving operations to an increasing number of patients with aortic regurgitation.

In patients with aortic aneurysms or dissections involving the aortic root, 2 reparative approaches have been used. The first consists of a remodeling operation with radical excision of all diseased aortic tissue down to the annulus followed by reconstruction of the root using 3 tongue-shaped processes to recreate the aortic sinuses (Figure 1A). Several modifications to reshape the sinuses have been suggested. The main advantage of the remodeling technique is the preservation of “distensibility” of the aortic root and the near-normal pattern of instantaneous movements of the aortic cusps. This may translate into clinical benefit in the longer term. However, there is concern about the reproducibility and durability of this type of repair. In the original series, starting in 1978 and incorporating the “learning curve,” the freedom from reoperation was 89% at 10 years. Progressive aortic regurgitation occurred only in patients with less than perfect results immediately after the operation. Appropriate timing of the operation before the onset of secondary changes in the cusps combined with technical refinements should minimize or abolish the need for reoperation. The technical refinements include slight undersizing of the Dacron tube (2 mm less than the echocardiographic measurements of the aortic root at the level of the attachment of the cusps) combined with the use of Long Dacron “lips” to recreate the longitudinal curvature of the sinuses. This results in creating vortices that prevent progressive dilatation of the sinuses by creating inward forces at the level of the attachment of the cusps. The second approach (the tube operation), introduced by David and Findel from Toronto, consists of less radical excision of the diseased aortic wall followed by insertion of the mobilized valve inside a Dacron tube (Figure 1B). The perceived advantage of this technique is the strong splinting of the valve mechanism by the surrounding Dacron tube, which is thought to enhance competence and prevent future dilatation. There is, however, some concern about the fact that the cusps can touch the Dacron tube and the effect of the absence of distensibility and sinuses of Valsalva on long-term valve function. Longer periods of follow-up are needed to establish the exact role of these operations.

The combination of ventricular septal defect and prolapsing aortic cusp has been the focus of attention for a relatively
shortening the free border of the prolapsing cusp. More recently, the realization that the basic abnormality in this syndrome is the discontinuity between the aortic media and the crest of the interventricular septum has resulted in the evolution of a simple technique of reattaching the interventricular septum to the media of the aorta using a series of interrupted mattress sutures (Figure 2). One of the advantages of this technique is that it does not involve touching the delicate aortic cusp tissue and therefore can be applied to infants before secondary changes in the valve occur.

Although the presence of bicuspid aortic valve predisposes to premature heavy calcification of the valve, a proportion of patients present with severe regurgitation with a pliable bicuspid valve. Some of these patients can be treated by repairing or redeveloping the fused commissure. The first technique consists of resecting a triangular part from the center of the fused redundant common leaflet to prevent its prolapse. An alternative technique consists of “recreating” the fused commissure by dividing the raphe and adding 2 triangular pieces of pericardium to reconstitute the commissure. This results in a competent trileaflet valve. A major disadvantage of this technique is that the material used for augmenting the cusps, whether autologous, homologous, or xenogenic, tends to shrink and calcify in the longer term. The same limitation applies to cusp augmentation.
used for repair of regurgitation of a tricuspid aortic valve\textsuperscript{38,39} in the presence of a pliable hinge mechanism.

In patients with pure aortic regurgitation secondary to rheumatic disease, the essential lesion is retraction of the cusps with preservation of the hinge mechanism. The hemodynamic lesion results in progressive dilation of the aortic annulus with worsening of the regurgitation. In these patients, cusp augmentation using 3 separate strips of biological material\textsuperscript{38,39} (Figure 3) may be effective for various periods of time. The size of the patch is critically important, and the use of large redundant patches, particularly in the region of the left coronary cusp, can result in the redundant patch being sucked into the left coronary orifice, which could be fatal.

Materials used for this purpose include autologous pericardium, either “fresh” or treated with 0.6% glutaraldehyde for 8 minutes, processed calf pericardium, or human dura mater processed with glycerin. The use of the latter material has been discontinued because of the risk of transmitting spongiform disease. The durability of the tissues is unpredictable in different patients. Recently, the Carpentier group has reported 92% freedom from reoperation at 5 years after this type of procedure.\textsuperscript{39} Development of tissue engineered living patches could enhance the durability of this operation.

Mitral Valve Repair

Despite the complexity of the mitral valve apparatus, this valve lends itself to repair in patients with both stenosis and regurgitation. Application of these techniques, however, depends largely on the pathogenesis of the valve disease, with >95% of patients with the floppy-valve syndrome being suitable for repair.

Rheumatic Mitral Stenosis

Until recently, closed transventricular mitral valvotomy, introduced by Andrew Logan in Edinburgh and perfected by O.S. Tubbs through the introduction of an adjustable transventricular dilation, has produced good early and midterm results and was cost-effective in developing countries. The availability of transcutaneous balloon valvuloplasty (PBV) or mechanical dilatation\textsuperscript{40} or open mitral valvotomy offers alternatives. The choice between these procedures depends on the morphology and function of the valve as well as economic and other factors. An echocardiographic scoring system was developed to assess the suitability for PBV.\textsuperscript{41} In a recent large series of PBVs from the Massachusetts General Hospital in Boston, the 12-year event-free survival after PBV was 38% for patients with an echocardiographic score of \( \geq 8 \), compared with 22% for those with an echocardiographic score of \( \leq 8 \).\textsuperscript{41} The use of transcatheter mechanical mitral commissurotomy with a metallic dilator (commissurotome)\textsuperscript{40} can give very good immediate results (procedural success of 93% in selected patients with either stenosis or restenosis).

Open mitral valvotomy\textsuperscript{42} is reserved for patients judged to be unsuitable for percutaneous procedures because of the presence of calcification, thrombus, or associated regurgitation. The operation consists of dealing with cusps, commissures, and subvalvar apparatus by use of fairly standardized techniques.\textsuperscript{42} The late results of this operation are good.\textsuperscript{42}

Rheumatic Mitral Regurgitation

Severe pure mitral regurgitation continues to affect a large number of children and young adults in the developing world.\textsuperscript{43} The most common structural cause of regurgitation in these patients is dilatation of the mitral annulus, sometimes associated with elongation of the chordae tendineae, particularly those fixing the anterior cusp.\textsuperscript{44} This can be associated with restriction of the posterior cusp. These abnormalities result in prolapse of the anterior leaflet and can be corrected by the insertion of a posterior annuloplasty band or ring extending from one trigone to the other, thus displacing the posterior annulus forward. This has the effect of preventing prolapse of the anterior cusp and producing good coaptation of the cusps. Before the annuloplasty is performed, the valve should be evaluated and additional abnormalities or defects should be dealt with. Because rheumatic affection of the
mitral valve produces progressive damage to the valve, the durability of this type of repair is not as good as repair of floppy valves. In a large series of 951 patients recently reported from Paris, with a follow-up of up to 29 years, freedom from reoperation was 89\% at 10 years and 82\% at 20 years.\textsuperscript{45}

Myxomatous Mitral Valve Disease (Barlow’s Syndrome)

This entity is currently the most common cause of pure mitral regurgitation in western countries, with a continued increase in its prevalence because of a variety of causes, including increased life expectancy. In this syndrome, mitral regurgitation is caused by prolapse of one or more segments of cusp tissue into the left atrium, resulting in a spectrum of clinicopathological syndromes.\textsuperscript{46,47} This is produced by elongated and/or ruptured chordae associated with voluminous leaflet tissue and dilated annulus. The flail segments are readily definable by 2D echocardiography and at operation. Patients with flail segments present with severe mitral regurgitation in >85\% of cases.\textsuperscript{47} The same authors have reported an increased mortality and morbidity in these patients even if they are asymptomatic or have relatively preserved left ventricular function. Sudden death accounted for approximately 25\% of deaths occurring under medical treatment in this series.\textsuperscript{48} This association needs to be confirmed and its causes investigated in a larger series of patients. Fortunately, the vast majority of these patients are amenable to repair, as mentioned earlier, by fairly standardized techniques.\textsuperscript{49–54} The most commonly affected region is the posterior cusp, which can easily be dealt with by quadrangular resection of the flail segment in combination with compression sutures to reduce the size of the annulus in this region or sliding plasty\textsuperscript{49} to reduce the incidence of systolic anterior motion of the mitral valve (Figure 4). Prolapse of the anterior cusp requires a more complex type\textsuperscript{50–52} of repair, which could involve triangular resection, insertion of artificial chordae, chordal translocation from the posterior cusp, or occasionally edge-to-edge repair as described by Alfieri and Maisano.\textsuperscript{52} The repair operation is usually combined with annuloplasty using a variety of semi-rigid rings\textsuperscript{53,54} designed to reduce and possibly reshape the annulus. Although annuloplasty is thought to “stabilize” the repair and possibly enhance its durability, to date there have been no prospective randomized trials to validate this point. In addition, this type of annuloplasty may interfere with the mobility of the mitral annulus or rarely produce systolic anterior movement\textsuperscript{54} of the mitral valve, which can occur in 4.5\% to 10\% of patients.

Despite the diffuse nature of the disease, the durability of repaired mitral regurgitation in patients with degenerative valve disease is excellent. In 2 large series,\textsuperscript{55,56} the freedom from reoperation at 10 to 15 years was 90\%.

The instantaneous hazard function for reoperation shows 2 phases, a peaking early hazard phase during the first year followed by a very low, slowly developing late phase.\textsuperscript{55} The cause of failure of the repair is technical reasons in approximately half of the patients,\textsuperscript{55} emphasizing the importance of experience and attention to detail in performing the repair, including the use of intraoperative transesophageal echo and ensuring lack of residual regurgitation at the time of operation. The incidence of postoperative endocarditis appears to be similar after repair compared with replacement. Several observational studies strongly suggest that long-term survival after repair is

Figure 5. Technique used for repair of TR due to Ebstein’s anomaly. A, Mobilization of anterosuperior leaflet. B, After division of abnormal chordae fixing ventricular aspect of leaflet to right ventricular wall, longitudinal plication of atrialized ventricle is started (A, B). C, Mobilized leaflet is reattached to its new position after completing plication of atrialized ventricle. Reprinted from Reference 80, with permission from the Society of Thoracic Surgeons.
superior to that after replacement, which has stimulated operation on all or most patients with severe regurgitation, provided that repair can be performed.

**Mitral Regurgitation Caused by Ischemic Heart Disease or Dilated Cardiomyopathy**

This type of mitral regurgitation defines a group of patients at high risk. A small proportion of patients present acutely after myocardial infarction with complete or partial rupture of one of the papillary muscles, usually the posterior. Patients with partial rupture of one of the heads of a papillary muscle can be treated by excision of the flail segment in a manner similar to that for floppy valves. In complete rupture, reattachment of the papillary muscle may be achieved in a minority of patients who have localized infarction affecting the attachment of the papillary muscle (a rare event); however, usually the only effective treatment is urgent valve replacement.

The most common cause of ischemic mitral regurgitation is associated with chronic heart failure caused by repeated infarction. Because the valve components are anatomically normal, this type of mitral regurgitation is often referred to as “functional mitral regurgitation.” The mechanisms responsible for “ischemic” functional mitral regurgitation are similar but not identical to those in mitral regurgitation associated with idiopathic dilated cardiomyopathy. Although this has been shown to be at least in part to be a result of dilatation of the mitral annulus, current evidence suggests that this is not the only factor and that one of the main causes of regurgitation in these patients is displacement of the papillary muscles downward and outward, thus leading to tethering of the mitral leaflets. Prognostically less severe degrees of functional mitral regurgitation, compared with mitral regurgitation caused by floppy-valve syndrome, have been shown to incur an excess mortality. Assessment of the severity of mitral regurgitation can be problematic, particularly perioperatively in patients under anesthesia or when the patients have been treated with intensive unloading therapy. When mild to moderate mitral regurgitation (effective regurgitant orifice of 20 mm²) is present preoperatively in patients requiring coronary artery bypass grafting, there is increasing evidence that this will not improve after revascularization and that it could have an adverse effect on long-term outcome. This supports the view that this degree of regurgitation should be repaired at the time of CABG. The use of an undersized annuloplasty is the most commonly performed method. Although this is effective, at least in the short term, it does not deal with the primary abnormality. Alfieri’s edge-to-edge repair has also been used in these patients. Other methods, such as septal-annular cinching and external plication and percutaneous repair have been used experimentally and may be useful clinically in the future.

In patients with functional mitral regurgitation who do not require revascularization, such as those with ischemic or idiopathic dilated cardiomyopathy, repair is considered only if regurgitation is judged to be severe.

**Mitral Regurgitation Caused by Acute Endocarditis**

Endocarditis of the mitral valve is the most common form of native heart valve endocarditis and carries a high morbidity and mortality in the acute phase. The most common organisms are Streptococcus veridans and Staphylococcus aureus and the enterococci. The disease results in various degrees of damage to the leaflets, chordae, and annular tissue and can cause abscesses involving the surrounding myocardium. Until recently, the condition was treated surgically only if intensive specific antibiotic therapy fails to control infection or if “uncontrolled” heart failure develops. The presence of large vegetations or abscesses did not necessarily constitute an indication for early surgical intervention. Recent evidence suggests that early repair could avoid excessive damage to the valve and give excellent long-term results. Repair usually consists of excision of infected tissue followed by direct reconstruction, as in the case of floppy-valve syndrome. More extensive damage to the valve could necessitate the use of autologous or xenogenic pericardium to repair defects in the leaflets, and artificial chordae may be used. The results of repair appear to be superior to those of replacement, in terms of both survival and incidence of complications or recurrence of infection.

**Tricuspid Valve Repair**

**Tricuspid Stenosis**

Isolated tricuspid stenosis is very rare and is usually part of rheumatic multivalvular disease. Although the hemodynamic lesion can be tolerated for long periods of time, the majority of patients require repair. At operation, the cusps are fused and produce a diaphragm-like structure; although the com-
missures can be identified and divided, the cusps are usually retracted and the subvalvar apparatus is affected. This necessitates the use of annuloplasty. Other forms of tricuspid stenosis are extremely rare.

Rheumatic Tricuspid Regurgitation

The most common cause of tricuspid regurgitation (TR) is functional TR secondary to rheumatic disease of left-sided valves, either before or after mitral valve operations.\textsuperscript{73–76} Although TR can regress after successful treatment of mitral valve disease, this is not always the case, with many patients having residual or progressive TR despite effective treatment of mitral valve disease with complete or partial normalization of the pulmonary artery pressure. TR in this setting can have adverse effects on clinical progress and outcome. Guidelines for repair\textsuperscript{73,75,76} of the valve include severity of TR assessed clinically and by imaging methods, indexed size of the tricuspid annulus ($>2.1\,\text{cm}^2$), ejection fraction of the tricuspid valve, and importantly, right ventricular function. Repair of the valve using ring, band, or suture annuloplasty is usually effective and does not increase the risk of the operation. In contrast, repair of isolated residual or recurrent TR after mitral valve surgery carries a higher risk (8.8% mortality).\textsuperscript{77}

Tricuspid Valve Endocarditis

Another lesion that can require tricuspid repair is tricuspid endocarditis from intravenous drug abuse or after long-term catheterization of the right side, such as in patients in an intensive care unit. It can also be treated with reparative techniques, such as pericardial remodeling of the annulus, total excision of the tricuspid valve, or annuloplasty. Finally, in an even smaller subset of patients, reparative procedures can be performed for lupus endocarditis, diet drug–induced valvulitis, or carcinoid of the tricuspid valve. In patients who require tricuspid valve replacement, right-sided bioprosthetic valves are generally indicated, because they last longer than the similar valve placed in the left side of the circulation.

Ebstein’s Anomaly

This anomaly comprises a spectrum of abnormalities\textsuperscript{78} that need to be defined and corrected if possible. Early attempts at repair of the tricuspid valve in Ebstein’s anomaly concentrated on “correcting” the downward displacement of the hinge mechanism of the septal and inferior leaflets into the right ventricle and obliterating the “atrialized” ventricle. More recent methods of repair\textsuperscript{79,80} (Figure 5) depend on creating a monocuspid valve using the reconstructed anterosuperior leaflet, which is almost always present as a large

\textbf{Figure 7.} Schematic views of device. Left, 3 parts of device are represented separately (from top: platinum stent, nitinol stent, and valve). Middle, Fully expanded device is shown longitudinally and axially. Right, diagrams demonstrate where nitinol and platinum stents are attached, which allowed stepwise approach. Reprinted with permission from Reference 85, Figure 2.

\textbf{Figure 8.} Illustrations of principle of use of a percutaneous device (inserted through coronary sinus) to correct functional mitral regurgitation. Courtesy of Viacor.
sail-like structure with adequate tissue for repair. It is equally important, however, to realize that this leaflet is highly abnormal (a fact recognized by Wilhelm Ebstein in his original article in 1866) in shape, location, and size with limited mobility because of the presence of abnormal chordae and the frequent direct attachment of the free border of the cusp to the right ventricular myocardium.79–80 These latter abnormalities can produce stenosis and abnormal orientation of the orifice of the valve. Vertical plication of the atrialized right ventricle as advocated by Carpentier and Chauvaud has the advantage of reducing the size of the annulus and the atrialized ventricle but carries a small risk of injuring the right coronary artery. This can be prevented by identifying that artery before performing the repair. Ebstein’s anomaly should be operated on only when there are hemodynamically significant abnormalities, because the milder forms of the disease are very well tolerated. Most patients operated on are amenable to repair with the addition of biventricular Glenn shunt, if necessary, but valve replacement is rarely required.

**Pulmonary Valve Repair**

Diseases of the pulmonary valve are usually caused by congenital abnormalities. Stenosis can be treated by balloon valvuloplasty, which produces very good early results.92 However, the longer-term outcome in these patients has not been formally compared with that obtained by surgical treatment. Although mild to moderate degrees of pulmonary regurgitation can be tolerated for a relatively long time, there is evidence that the condition is not entirely benign and can cause right ventricular dysfunction93 and/or arrhythmias and therefore may have an adverse effect on symptomatic status and possibly survival. In these patients, pulmonary valve replacement with a pulmonary allograft is the treatment of choice. Very few of these valves are amenable to repair.

**Percutaneous Repair of Valve Regurgitation**

As outlined earlier, percutaneous relief of valve stenosis by balloon dilatation or mechanical devices is being applied routinely in selected patients with mitral, pulmonary, and aortic stenosis. More recently, percutaneous techniques for treating pulmonary regurgitation by insertion of a bovine jugular vein inside a stent have been developed and applied clinically44 (Figure 6). Although similar techniques are being developed for treating aortic regurgitation45 (Figure 7), this is more problematic because of the proximity of the coronary ostia coupled with exposure to high pressure.

Percutaneous devices for treatment of functional mitral regurgitation introduced into the coronary sinus have been developed and tested in experimental models46 (Figure 8) with encouraging results.

**The Future**

Rapid progress in our understanding of the sophisticated functions of heart valves should lead to continued efforts to reproduce these functions at the cellular, molecular, and integrated tissue levels. This may be achieved through the development of novel reparative techniques or valve replacement using tissue-engineered substitutes. The ultimate aim is to restore both longevity and quality of life to normal after what is in effect a timely “corrective” operation.

**References**

Novel Approaches to Cardiac Valve Repair: From Structure to Function: Part II
Magdi H. Yacoub and Lawrence H. Cohn

doi: 10.1161/01.CIR.0000115634.66549.4D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/109/9/1064

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/