Biventricular resynchronization, a therapy recommended for patients presenting with left ventricular (LV) dysfunction and ventricular dyssynchrony, requires the implantation of an LV lead, usually placed in a lateral or posterolateral tributary of the coronary sinus. Despite important progress made in the development of dedicated instrumentation, the procedure remains sometimes challenging and unsuccessful in a minority of patients. In the rare instances of unsuccessful transvenous implantations occurring in the presence of major surgical contraindications, a few operators have implanted the LV lead transseptally, an approach limited by technical difficulties and by the thromboembolic risk associated with the presence of a lead inside the LV cavity. The interest in this approach was recently renewed by 2 studies in an animal model and in humans, respectively, which both found a distinctly superior hemodynamic performance associated with endocardial compared with epicardial stimulation. This review discusses the advantages and disadvantages of LV endocardial stimulation, examines the various techniques of LV endocardial stimulation, and projects their future applications in light of these highly promising recent results. The implementation of endocardial stimulation will ultimately depend on: 1) the development of safe, effective, and durable instrumentation, and reliable and reproducible intraprocedural methods to identify the optimal site of stimulation; and 2) the completion of controlled trials confirming the superiority of this technique compared with standard cardiac resynchronization therapy. (J Am Coll Cardiol 2010;56:747–53) © 2010 by the American College of Cardiology Foundation

A review of the literature suggests that <100 patients have undergone transseptal procedures, which remain limited by technical difficulties due to the lack of appropriate instrumentation and by the thromboembolic risk associated with the presence of a lead inside the LV cavity. Despite these limitations, this technique has several advantages, including: 1) access to all regions of the left ventricle; 2) a faster impulse propagation in the endocardial than in the epicardial ventricular layers, allowing, at least theoretically, a faster LV depolarization; and 3) an apparently more physiologic LV stimulation, preserving the transmural activation and repolarization sequence. The interest in this approach was recently renewed by 2 studies, which reported a distinct hemodynamic superiority associated with endocardial stimulation compared with epicardial stimulation (17,18). Since the main limitation of cardiac resynchronization therapy (CRT) is the predictable proportion of nonresponders, any new technique allowing a lowering of the percentage of nonresponders is welcome. The importance of the results of these 2 studies raises the issue of alternatives to coronary sinus pacing, including the future role of LV endocardial stimulation in candidates for CRT. This review discusses the advantages and disadvantages of LV endocardial stimulation, examines the various techniques
of LV endocardial stimulation, and projects their future applications in light of these highly promising recent results.

Rationale for LV Endocardial Pacing

Limiting factors. Transseptal, transapical, and transaortic stimulation are techniques limited by thromboembolic complications and by complex repeat procedures to manage lead infections or fractures. Furthermore, the implantation of a transseptal lead adds the risks associated with its position across the mitral valve. Thromboembolic complications. The risk of thrombus on the lead, which may form regardless of the lead position inside the cardiovascular system, is a major concern with this type of technique (19). Embolization from a right ventricular lead is the cause of pulmonary embolism (20). However, embolization from the left ventricle is the source of considerably more serious systemic complications, including cerebrovascular accident. In addition, the presence of an atrial septal orifice may be the source of paradoxical embolization, facilitated by pulmonary hypertension, often present in patients suffering from heart failure.

The few patients who have undergone the deliberate implantation of LV endocardial leads all received heparin during the procedure, and systemic anticoagulation therapy for the long term. While their low number precludes the drawing of firm conclusions, 2 cases of thromboembolic complications have been reported after the inappropriate discontinuation of anticoagulation therapy by the patients (9,10). In contrast, large numbers have been reported of inadvertent implantation of LV stimulation lead through a patent foramen ovale. In a review of the literature, van Gelder et al. (21) found that the diagnosis of lead misplacement was made after thromboembolic complications in approximately one-third of cases. It is likely, however, that some asymptomatic patients who received LV endocardial leads remained undetected, and that complications associated with accidental implantations of endocardial leads are under-reported, as implanting physicians might not willingly declare their failures. Therefore, the true incidence of thromboembolic complications associated with the inadvertent implantation of a lead inside the left ventricle is unknown. Furthermore, since these implants are involun- tary and undetected, the majority of these patients are not given anticoagulation therapy.

The risks associated with the implantation of an LV stimulation lead mandates several precautionary measures. First, the implantation procedure must be performed during effective heparinization, increasing the risk of post-procedural hematoma, and mandating meticulous hemostasis with an electric scalpel. Second, long-term systemic anticoagulation therapy must be instituted, with its risks of inappropriate discontinuation or excessive doses and hemorrhagic complications. The level of anticoagulation representing an optimal compromise between hemorrhagic and thrombogenic risk remains to be defined, and the development of new anticoagulants might facilitate the long-term care of these patients. Third, instrumentation must be chosen that has the lowest thrombogenic properties. Thin leads made of polyurethane might be preferred. Fourth, during transseptal catheterization, a precise concordance between the size of the lead and that of the interatrial septal orifice might facilitate the closure of the interatrial communication and lower the risk of paradoxical embolization.

Interaction with the mitral valve. An LV lead implanted by the atrial transseptal approach crosses the mitral valve (Fig. 1). The interference of the lead with the valve, including increased risk of insufficiency and endocarditis in case of infectious complications, may be a major concern. Tricuspid insufficiency sometimes complicates the implantation of leads in the right ventricle. Recipients of CRT systems often present with variable degrees of mitral insufficiency due to ischemic heart disease or annular dilation. The few case reports of transseptal lead implantation have not described an increase in the grade of mitral insufficiency (8–16). The use of thin leads might lower the risk of interference between lead and valve.

However, the risk of mitral valve endocarditis is a considerably greater concern, particularly with the rise in the incidence of infections observed in recent years. The contact of an infected lead with the valve may promote the development of mitral valve endocarditis, as occurs with the tricuspid valve, exposing the patient to systemic embolization of vegetations. The risks of secondary infectious foci and cerebral or renal abscess appear far greater than the risks
associated with similar complications occurring in the right side of the heart. The need to proceed with surgical treatment of the mitral valve may have catastrophic consequences when performed in patients in severe heart failure, at highest operative risk.

**Risks associated with extraction of the cardiac resynchronization system.** Because of the risk of systemic embolization of vegetations, thrombi, or fibrous material surrounding the lead, percutaneous procedures seem excessively risky. The standard instrumentation available is poorly adapted to extract LV endocardial leads, notably with its lack of valves to prevent the introduction of air during the procedure. Furthermore, as described with the tricuspid valve during lead extractions from the right heart, the procedure might be complicated by serious injury inflicted to the interatrial septum and the mitral valve (22). A surgical intervention would, therefore, have to be performed systematically, despite the few published reports of uncomplicated percutaneous extractions (23).

**Advantages of LV Endocardial Stimulation**

Despite the significant limitations described earlier, compared with the standard approach through the coronary sinus, LV endocardial stimulation offers several notable advantages. First, the transseptal access allows a choice of the site of stimulation, as opposed to a lead implant through the coronary sinus, where the site is often imposed by anatomical constraints. This choice allows an optimization of the capture threshold, a step that might be challenging when the lead is placed in a coronary sinus tributary. In presence of a high capture threshold, the lead can easily be maneuvered to a different site, which is often technically difficult inside the cardiac venous network. Phrenic nerve stimulation is not a concern, as a wide choice of sites is available. Furthermore, the incidence of lead dislodgement should be lower than when the lead is in a cardiac vein, and be similar to that observed after the implantation of active fixation leads in the right atrium or ventricle.

Second, the monitoring of cardiac function by a sensor imbedded in the stimulating lead is the object of active research (24,25). The prevention of cardiac decompensation is a priority for individual patients and for public health in general. The data are currently acquired by a lead placed in the right ventricle, providing indirect information with respect to LV contraction. The implantation of a lead inside the left ventricle allows the direct measurement of LV contraction, which better reflects the hemodynamic status, allowing more precise adjustments in case of progressive degradation of contractile function, and a more accurate prediction and prevention of cardiac decompensation.

Third, LV endocardial stimulation appears more physiologic and might be less arrhythmogenic than epicardial stimulation. In some patients, the onset of LV epicardial stimulation causes the development of polymorphous ventricular arrhythmias, as it reverses the transmural activation sequence and delays the depolarization and repolarization of the endocardium (26–28). In animal models, this reversal is the source of heterogeneous conduction and increased transmural dispersion of repolarization, which is a mechanism of re-entrant arrhythmias. The shift from endocardial toward epicardial stimulation increases the transmural dispersion of repolarization and the duration of the QT interval and, in vulnerable patients, increases the risk of developing torsades de pointes. A normal transmural activation sequence associated with LV endocardial simulation might, therefore, lower the risk of developing arrhythmias.

Fourth, standard biventricular resynchronization is associated with a predictable approximately 30% rate of nonresponse to therapy. Thus far, a single study, conducted in our institution, compared 17 recipients of leads implanted through the coronary sinus with 8 patients stimulated through transeptal LV endocardial leads (29). At 6 months of follow-up, echocardiography showed less ventricular dyssynchrony, greater LV shortening fraction, and a higher velocity-time integral with endocardial than with epicardial LV stimulation. The conclusions of this limited, nonrandomized study must be interpreted cautiously.

**Confirmation of the superiority of endocardial stimulation in the dog.** A recent hemodynamic study by van Deursen et al. (17), which showed a highly significant superiority of LV endocardial compared with epicardial stimulation, rekindled the interest in this treatment method. In 8 dogs, which had undergone ablation of the left bundle branch, hemodynamic function associated with single-site LV stimulation was compared with that associated with biventricular stimulation using 8 LV epicardial sites and 8 corresponding LV endocardial sites. The measurements included maximum and minimum rate of increase of LV pressure (dP/dt_max, dP/dt_min), stroke work, electrical dyssynchrony, and dispersion of repolarization. Several observations were made in this study. First, compared with epicardial, endocardial stimulation was associated with more normal activation, mitigating the overall and transmural dispersion of repolarization, and preserved the physiologic direction of activation from endocardium to epicardium. Although not an objective of this study, its results suggested that, as previously published, endocardial stimulation might be less arrhythmogenic than epicardial stimulation. Second, as observed previously, epicardial stimulation, compared with spontaneous rhythm, mitigated ventricular dyssynchrony and shortened the duration of ventricular activation. Endocardial stimulation conferred additional benefits, and further shortened significantly the duration of ventricular activation and QRS complex. This greater mitigation of ventricular dyssynchrony by endocardial stimulation, an effect probably key in the long-term outcome of CRT, could be explained by a faster endocardial than epicardial conduction and a smaller, central endocardial than epicardial circumference. Third, compared with the corresponding epicardial site, endocardial stimulation was associated with a 90% increase in dP/dt_max and 50% increase in stroke work.
stimulating at the LV epicardium, wide variations in the hemodynamic response were observed depending on the site of stimulation, with a significantly greater benefit conferred by apical compared with basal stimulation. In contrast, the hemodynamic response was similar among the various endocardial sites of stimulation that were tested. Likewise, the hemodynamic benefit was less dependent on the optimization of the atrioventricular delay when stimulating from the endocardium than from the epicardium.

Although this study was performed in a model of acute left bundle branch block relatively distant from the clinical and electrophysiologic characteristics of patients with heart failure, its results are important and show unequivocally the superiority of endocardial stimulation on hemodynamic measurements measured invasively. They need to be confirmed in an animal model of chronic heart failure with cardiac dyssynchrony, then in patients who are candidates for CRT.

**Short-term hemodynamic study of endocardial stimulation in patients with heart failure.** We recently completed a short-term hemodynamic study that compared standard epicardial stimulation through the coronary sinus with LV endocardial stimulation (18). To study a homogeneous population, we included 35 patients presenting with non-ischemic cardiomyopathies and with the usual criteria for the implantation of a CRT system. They underwent hemodynamic studies to compare \( \frac{dP}{dt_{\text{max}}} \), \( \frac{dP}{dt_{\text{min}}} \), pulse pressure, and LV end-diastolic pressure during single-site LV stimulation from the base, the mid–endocardial septum, the anterior, lateral, and inferior endocardial walls, and from the epicardial lateral wall through the coronary sinus and its opposite endocardial site. The results of this comparative study are important. First, we found a wide interindividual disparity in the location of the optimal versus least favorable site of stimulation, such that a predictably best, or least favorable, site was not identified for all patients. Instead, the distribution of optimal or least favorable sites was relatively even among the 11 sites tested. For example, LV epicardial stimulation was associated with the greatest hemodynamic benefit in 9% of patients and the least benefit in 17% of patients. Second, the choice of stimulation site had variable effects among CRT recipients. Whereas in some patients the hemodynamic variations were modest regardless of the site tested, major intrapatient variations were observed in other patients, depending on the site of stimulation, with, in some cases, opposite responses, such that \( \frac{dP}{dt_{\text{max}}} \) was decreased by stimulation at 1 site and markedly increased at another. Third, on average, optimization of the site of stimulation contributed a significant benefit to all measurements made. Stimulation of the lateral wall from a coronary sinus tributary was associated, on average, with a 15% increase compared with control rhythm, versus 30% when stimulating at the optimal site. Therefore, a search for an optimal site allowed a doubling of the hemodynamic benefits compared with standard epicardial stimulation of the lateral LV wall. These observations are important for patients who derive no hemodynamic benefit from epicardial LV lateral wall stimulation, in whom at least 1 site might be successful. Fourth, we found that approximately 10% of patients are not improved regardless of the site of stimulation, perhaps representing the true short-term nonresponders to CRT. Fifth, the comparison between epicardial and endocardial stimulation at a same site showed a significant benefit contributed by endocardial stimulation on diastolic \( \frac{dP}{dt_{\text{min}}} \), but not systolic \( \frac{dP}{dt_{\text{max}}} \) function.

These 2 studies, respectively conducted in dogs and humans, yielded both similar and different results, the latter explained by different protocols. We did not study biventricular stimulation. Furthermore, patients presenting with heart failure and cardiac dyssynchrony are considerably different from a short-term animal model of dyssynchrony without heart failure. While, in our study, the hemodynamic response hinged on the choice of stimulation site, it was similar regardless of the endocardial site tested in the animal model. In addition, when comparing endocardial and epicardial stimulation at a similar site, we observed a benefit limited to diastolic function, whereas diastolic and systolic function were both improved in the animal model. Ultimately, in both studies, LV endocardial stimulation and a search for an optimal site both allowed a highly significant and immediate improvement in systolic and diastolic function compared with standard LV epicardial stimulation.

**Technical Considerations**

**Transseptal LV endocardial stimulation.** The placement of a transseptal LV endocardial lead requires the puncture of the interatrial septum, to allow the passage of the lead from the right to the left atrium before entering the left ventricle through the mitral valve. The implantation of a permanent transseptal LV stimulation lead has been described, using the superior, the inferior, or a mixed approach. We described, in 1998, the first case of permanent transseptal LV stimulation, using a mixed right internal jugular and femoral approach (8). The proximal segment of a guidewire, placed in the left atrium through a transseptal puncture performed from the femoral vein, was snared by a loop advanced from the jugular vein. A sheath was introduced into the left atrium along the guidewire, and the stimulation lead was advanced through the sheath. The technical challenges represented by this procedure prompted us, along with another group of French investigators, to proceed with the puncture of the interatrial septum directly from the right internal jugular vein (9,10). The instrumentation used was not dedicated to this procedure, and was adapted to comply with the individual, anatomic circumstances. The septum was punctured with or without the guidance of transesophageal echocardiography, with a needle preformed to reach the fossa ovalis. The lead was tunneled subcutaneously to a pre–pectoral pocket (Fig. 2). This internal jugular approach is limited by the challenge represented by the absence of typical anatomic landmarks to localize the fossa ovalis, and
by the tunnelization, with its risks of cutaneous erosion or lead damage.

The transseptal catheterization of the left atrium is a technique familiar to electrophysiologists, used to perform ablations of accessory pathways, ventricular tachyarrhythmias and, more recently, pulmonary veins isolation (30–32). The septum is punctured from an inferior approach, using the right femoral vein. Several operators have developed a mixed approach, with the transseptal puncture performed from the right femoral vein, and implantation of the lead from the subclavian vein (11–14). The septum is punctured with a needle or by delivery of radiofrequency energy, and a balloon may be used to dilate the orifice and facilitate the passage of the lead. A wire is placed in the left atrium, serving as a guide for the introduction of the stimulation lead through a deflectable sheath. Regardless of the techniques implemented, the procedural success is high, the complication rate is low, and the results published regarding the long-term stability of the lead and capture threshold are encouraging.

**Transaortic LV endocardial stimulation.** Hungarian investigators have recently described transapical LV endocardial stimulation through limited thoracotomy (36). Using Seldinger’s technique, active fixation leads were introduced into the LV cavity by puncturing the apex, positioned under fluoroscopic guidance, fixed to the endocardium, and tunneled toward the pulse generator pocket. Since the leads did not cross the mitral orifice, the risk of valvular insufficiency was eliminated. The long-term safety and efficacy of this technique, performed in a limited number of patients, need to be examined in larger studies.

**Future Perspectives**

The observations made in these 2 recent studies might reopen the conversation around the future role of LV endocardial stimulation, from which various patient populations could theoretically benefit. First, this could benefit patients in whom the standard epicardial approach has failed, who are at prohibitive surgical risk, and who represent the majority of current recipients of endocardial leads. Second, this could benefit the 30% of nonresponders to standard CRT, who are in refractory heart failure and in a therapeutic dead end, without alternate management option. While these recent observations suggest that endocardial stimulation can improve hemodynamic function considerably and immediately, it remains to be confirmed that it will be associated with a clinical benefit, keeping in mind that, in our study, some patients whose dP/dt\text{max} was not increased by standard LV epicardial, lateral wall stimulation had a $>80\%$ increase when stimulated from the endocardium. In the regular absence of alternate treatment available for these patients, it appears legitimate to consider the planning of a trial to validate this strategy, as the expected benefit seems to prevail over the disadvantages represented.
by long-term anticoagulation therapy. Third, the deliberate implantation of an endocardial lead during a first implant of a CRT system deserves consideration. However, dedicated instrumentation needs first to be developed to facilitate the implant procedure and more broadly disseminate this strategy. For the transseptal approach, instruments must be designed to allow the lead implantation in a single stage from the subclavian vein. Transapical lead implants are also limited by the need to anticoagulate on the long-term. One might, however, conceive new surgically implanted epicardial leads, of which the stimulation electrode only would traverse the LV wall to stimulate the endocardium.

It is noteworthy that one cannot expect to eliminate all nonresponders because, in some patients, the response to endocardial stimulation remained weak regardless of the site tested. Our results, however, suggest that the optimization of the site of stimulation is an essential step, for which the best invasive or noninvasive hemodynamic measurement will need to be defined, though no consensus has, thus far, been reached with respect to which measurement best predicts a clinical response.

Leadless pacing may considerably change the technical challenges confronting the implanting physicians (37). Work in progress with prototypes implanted in animals appears promising. While this new instrumentation will completely change the technical aspects of the implant procedures, the issue of stimulation site will persist and, in the case of devices implanted with a view to improve hemodynamic function and alleviate the manifestations of heart failure, the search for an optimal site will continue, and the putative superiority of LV endocardial versus epicardial stimulation will remain a key question.

Conclusions

The implementation of endocardial stimulation will ultimately depend on the development of instrumentation that is safe and effective in the long term, on the development of reliable and reproducible methods to identify the optimal site of stimulation during the procedure, and on the completion of controlled trials confirming the superiority of this technique compared with standard CRT.

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