Trans-Coronary-Venous Interventions

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Abstract—The coronary venous system is routinely targeted during electrophysiological measurements or cardiac resynchronization therapy. However, several novel interventional techniques require coronary venous catheterization and visualization as well as transvenous delivery of devices and/or therapeutic agents. Recent reports suggest the possibility of a transvenous approach for the interventional treatment of refractory angina and mitral valve regurgitation. In addition, the coronary venous system has been used as a route for the delivery of stem cells in patients with left ventricular dysfunction due to ischemic heart disease. We review the potential value of using a coronary venous approach in association with recent therapeutic developments in the interventional treatment of structural and ischemic heart disease. We will also discuss techniques related to coronary venous catheterization. (Circ Cardiovasc Intervent. 2008;1:134-142.)

Key Words: catheterization ■ catheters ■ valves ■ valvuloplasty ■ veins

More than a century ago, Pratt1 first described the use of coronary veins to deliver arterial blood to ischemic myocardium. His experiments showed that the coronary veins could be used as conduits for oxygenated blood and could preserve myocardial viability in the absence of normal arterial perfusion. Early in the 20th century, Beck described a procedure to treat patients with severe angina. Coronary venous pressures were elevated by surgically narrowing the coronary sinus (CS) in association with a partial pericardectomy.2–4 This procedure known as the Beck I procedure was later modified to include a vein graft from the descending aorta to the great cardiac vein and partial ligation of the CS. Thus, in the Beck II procedure, the coronary venous system was partially arterialized. Several patients reported relief from anginal symptoms. These elegant operations were performed many years before the first coronary artery bypass graft surgeries and without the aid of cardiopulmonary bypass equipment. However, with the introduction of coronary artery bypass surgery and because of the long-term complications resulting from permanent obstruction of venous drainage including CS thrombosis, late myocardial hemorrhage, venous engorgement, edema, and subsequent fibrosis, these techniques were abandoned in the mid-1970s.

Because of the enormous progress in the treatment of ischemic heart disease in the second half of the 20th century, there is a growing population of patients with chronic heart disease, severely altered contractile function, refractory ischemia, and/or functional mitral regurgitation (MR) who are not good candidates for surgery.

Recently, several techniques using coronary venous access have been developed for targeted delivery of pharmacological agents, mechanical devices, or stem cells.

In this study, we review the anatomy of the coronary venous system and focus on its potential value for new therapeutic approaches in invasive cardiology. The use of the coronary venous system for routine electrophysiological procedures is out of the scope of this article.

Coronary Venous Anatomy and Its Imaging

The coronary venous anatomy is marked by 2 important features. The first is its high variability among patients in terms of number, size, tortuosity, and location of veins. The second is a high number of anastomoses between branches such that the occlusion of one branch does not compromise overall venous return.

There are several published studies on cardiac vein anatomy that introduce the nomenclature used in routine practice.5–8

The anterior interventricular vein (AIV) usually originates at the lower or middle third of anterior interventricular groove and runs parallel to the left anterior descending artery to the base of the heart. At the atroventricular groove, it turns posteriorly and becomes the great cardiac vein. The great cardiac vein lies adjacent to the circumflex artery and receives variable numbers of tributaries from the surface of left ventricle (Figure 1). The great cardiac vein joins the CS where the very small oblique vein of the left atrium, an embryological remnant called the vein of Marshal, drains into the CS. At this point, an internal paired valve is often present (valve of Vaeussens). At the posterior interventricular groove, the posterior interventricular vein (PIV) runs near the posterior descending artery. The PIV originates at the apex of the heart and terminates at the base, usually draining into CS

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close to its ostium in the right atrium. The name PIV was recently adopted by Nomina Anatomica as described by von Lüdinghausen and replaces the middle cardiac vein frequently used in the past. The AIV and PIV have been found in nearly every patient (99% and 100%, respectively).

The left marginal veins and the posterior veins of the left ventricle run between the AIV and PIV at the lateral or posterior aspect of the left ventricle (Figure 1). They drain into the great cardiac vein or straight into the CS. The numbers of these veins are variable, but at least one large left marginal vein is present in 99% of patients. It has been recently suggested by Van de Veire et al that the presence of the large marginal vein can be modified in patients with a history of myocardial infarction. In their study, a series of 100 patients were imaged using 64-slice multislice computer tomography (MSCT). Subjects were divided into 3 groups: 28 control patients, 38 patients with significant coronary artery disease, and 34 patients with a history of infarction. None of the patients with lateral infarction and only 22% of patients with anterior infarction had the left marginal vein.

A large number of small veins comprise a separate network called Thebesian system. These vessels drain the myocardium and empty directly into the heart chambers, mostly the right atrium.

A segmental classification of coronary venous system was recently proposed by Singh et al to identify and match the location of the left-sided venous tree to the underlying left ventricular myocardial segment.

Retrograde venography via the CS is the standard technique for the coronary vein visualization and defining venous anatomy. It is performed by cannulation of the CS from a subclavian, jugular, or femoral entry site. To help visualization of the CS ostium before its cannulation, the venous phase of coronary arterial angiography in LAO 30° cranial seems to be the best choice (Figures 1B, 2B, 4A, and 4B). CS cannulation from the jugular approach requires advancement of the catheter to the ostium level and counterclockwise catheter rotation to obtain coaxial intubation of the CS. Several catheter shapes may be used for successful CS cannulation from the jugular approach, including multipurpose and Sones catheters. Cannulation of the CS from the femoral approach is much more difficult and therefore less frequently used. Amplatz left, SIM-1 or similar shape catheters are advanced to right atrium at the CS ostium level and rotated clockwise to cannulate the CS. Withdrawal of Amplatz-like shape catheters from the CS is commonly difficult and requires movement of the catheter tip upwards and subsequent introduction of the tip into right ventricle, which allows for straightening of the catheter for later withdrawal to the femoral vein. Several trans-coronary-venous interventions require deep cannulation with large 9F or 10F guiding catheters. We strongly recommend not to advance a “naked” guiding catheter into the coronary venous system because it may cause venous dissection or perforation. The majority of dedicated CS guiding catheters can be advanced over a smaller, soft-tip 6F or 7F catheter introduced over a wire (Figure 4A). For the femoral approach, withdrawal of the guiding catheter should also be performed over a smaller catheter because upward movement of the guiding catheter usually causes excessive tension on the vein wall.

Venography is obtained by a direct injection of the contrast agent in the upstream direction (retrograde venography). To optimize venous imaging, the injection is sometimes performed while an occlusion balloon is inflated in the lumen of the CS to slow down the blood return to the right atrium (Figure 1B). The venograms are then usually taken in RAO 30°, AP and LAO 30° cranial or caudal views. Data from previous studies indicate that using this technique allows the distal coronary venous system to be visualized in most of the cases. Although, in some cases, the presence of venous valves blocks the backward flow of the contrast medium. Additionally, indirect visualization of the veins can be obtained shortly after retrograde venography. About 5 to 10 seconds after a contrast injection, the veins fill with contrast.
Coronary Venous System-Based Interventions
Treatment of Myocardial Ischemia

Although revascularization procedures by percutaneous interventions or bypass surgery are largely used in the treatment of patients with ischemic heart disease, there remain a relatively large number of patients with refractory angina. Their number is estimated at 5% to 10% of all patients with angina and may include 100,000 individuals in the United States alone. In patients with chronic refractory ischemia, 2 treatment options are available. The first option is the use of coronary bypass surgery, and the second option is the use of retrograde drug administration via the coronary venous system.

The coronary venous system has been also evaluated as a potential route for drug administration. Many animal studies have evaluated the efficacy of retrograde infusion of drugs into the coronary venous system. In one study, SRP was associated with a reduction in the number and severity of angina episodes and the use of nitroglycerine in patients with unstable angina. SRP has also been reported to improve ventricular contractility, prevent the onset of cardiacogenic shock, and reduce ST segment changes in humans with severe ischemia. Finally, SRP has been found to preserve myocardial viability and limit experimentally induced infarct size. Clinical application of this treatment modality has been progressively limited by the increasing use of stents in interventional cardiology. The technique of retrograde venous perfusion is now common only in heart surgery with cardiopulmonary bypass and is used to supply myocardium with protective cardioplegia.

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The initial human experience with catheter-based coronary venous arterialization has been reported by Oesterle et al.\textsuperscript{50} This procedure has been termed percutaneous in situ coronary venous arterialization. A series of specialized catheters and implantable devices are required to perform the percutaneous in situ coronary venous arterialization procedure. These catheter-based devices can be divided into 4 categories: CS and subselective guiding catheters, transaccess catheters equipped with an integrated ultrasound guidance system, flow-directing/blocking devices, and channel creation and maintenance devices. The most important part of the procedure is the creation of a junction between the artery and the parallel vein, proximal to the arterial occlusion. There is also another technique in which placement of the second communicator between the vein and the artery, distally to the arterial occlusion creates a bypass conduit around the arterial lesion. This procedure is called percutaneous in situ coronary bypass.\textsuperscript{50} Although both of these techniques have been suggested to be very promising, many questions remain. The efficacy, safety, clinical benefit, and durability of the bypasses still need to be established.

Another technique to alleviate myocardial ischemia using the coronary venous system has been recently tested in humans by Banai et al.\textsuperscript{51} They developed a device called CS reducer stent, which is designed to create CS narrowing and to elevate CS pressure. The initial experience in 15 patients with refractory ischemia shows a reduction in angina score and improvement in stress-induced ST depression and the extent of myocardial ischemia assessed by dobutamine echocardiography or thallium-201 single-photon emission computed tomography imaging.

**Trans-Coronary-Venous Cell Transplantation for Myocardial Regeneration**

Congestive heart failure resulting from a loss of myocardial tissue subsequent to acute myocardial infarction still remains an important clinical problem. Patients with no viable myocardium in the area of postinfarction injury as indicated by MRI, scintigraphic methods, or stress echocardiography cannot benefit from revascularization. Percutaneous coronary interventions or bypass surgery can only restore hibernating myocardium. The experimental data from animal studies suggests that transplantation of autologous myocyte precursors (myoblasts) into a postinfarcted area may improve ventricular function and prevent negative remodeling.\textsuperscript{52–56} The first autologous skeletal myoblast transplantations in humans were performed during bypass surgery.\textsuperscript{57–60} The procedures were found to be safe, and a mild increase in ejection fraction in study patients was noted after 6 and 12 months. Although, it has been difficult to assess whether the increased contractility of the left ventricle resulted from the simultaneous coronary revascularization or implantation of the cells independently. To resolve this problem and reduce the invasiveness of cell delivery in the treatment of postinfarction heart failure, percutaneous autologous myoblast transplantation was introduced by Smits et al\textsuperscript{60} using an endoventricular approach and the NOGA-guided catheter system. It should be pointed out that currently available endoventricular catheter systems have limited stability, because the catheter does not follow the heart movements. With the endoventricular systems, the injection needle is directed perpendicularly to the inner surface of the cardiac muscle wall. Thinned postinfarction scar should be considered a relative contraindication. In addition, the injection pressure with the endoventricular systems can be destabilizing and cause expulsion of the needle tip from the injection site.

To overcome the potential limitations of the endoventricular techniques, Siminiak et al\textsuperscript{58,59} have introduced cell transplantation performed via cardiac veins. The first series of patients to have percutaneous autologous myoblast transplantation were in the POZNAN trial. The trial was a phase I clinical trial for both a transvenous coronary catheter system and myoblast transplantation performed as a sole procedure (ie, without concomitant revascularization). The procedures were performed via the right femoral venous approach using an 11F vein introducer. The CS was successfully cannulated with a 10F guiding catheter (Figures 2 and 3). For visualization of the coronary venous system, the retrograde venous injection of contrast medium was used along with simultaneous inflation of a balloon located at the tip of CS guiding catheter. From the guiding catheter, a hydrophilic floppy guidewire was advanced either through the great cardiac vein to the distal part of the AIV (Figure 2) or straight to the PIV (Figure 3). Then a novel monorail TransAccess catheter (Trans-Vascular Inc, Menlo Park, Calif) with an intravascular ultrasound probe and a hook-shaped needle at its end was advanced over the wire to the target akinetic area of myocardium. The intravascular orientation was achieved using the parallel running artery, ventricular muscle, and pericardium as landmarks, which are all well appreciated with ultrasound imaging. After intravascular ultrasound confirmation of the position, fluoroscopic guid-
ance was used to advance the hook-shaped needle from the lumen of the coronary vein toward the target area. Thereafter, the microinfusion catheter (IntraLume, Transvascular) was advanced through the needle toward the scar of myocardium (Figures 2C and 3C). Two to 4-infusion channels were created for the delivery of up to 100 million cells in 0.4 to 2.5 mL of saline. The myoblast cells were transplanted in long tracks from 1.5 to 4.5 cm during the microinfusion catheter advancement. That allowed deposition of the cells into a potentially large area of heart muscle with a limited number of venous punctures. Furthermore, because of the pressure of the liquid injection in front of the advancing microcatheter, the myocardial trauma seemed to be minimal. There were no significant elevations in troponin levels noted after the procedures.

This study showed that the percutaneous approach into an infarct area of myocardium using the coronary venous system is safe and feasible in most patients. The lack of procedural success in one patient was related to the inability to appropriately position the guiding catheter in the CS. This technique seems suitable even for thin postinfarction scars because with the TransAccess system, the injections are made parallel to the ventricular wall. Despite the high variability in the coronary venous system, it was possible to reach even remote areas of the cardiac apex. Surprisingly, in the POZNAN trial, the PIV was shown to be a better route for cell delivery to the apex than the AIV (Figure 3). The percutaneous autologous skeletal myoblast injection technique without simultaneous revascularization allows for evaluation of the effects of the injections on ventricular contractility. In this study group, New York Heart Association class improved in all patients over the 6-month follow-up period. Global left ventricular ejection fraction increased from 3% to 8% in 6 of 9 cases. A better understanding of the possible benefits of this procedure for the treatment of postinfarction heart failure requires further investigation.

Percutaneous Transvenous Mitral Annuloplasty

Degenerative MR is the most common cause in Europe, whereas ischemic and functional MR are increasingly frequent. MR is now the second most frequent valve disease after aortic stenosis. MR severity is an independent predictor of clinical outcome in patients with ischemic heart disease, even when MR is moderate or mild, and particularly in the presence of congestive heart failure. In severe MR, prognosis is poor even if the patient is asymptomatic. MR is common after myocardial infarction and may lead to progressive ventricular and annular dilation, worsening of regurgitation and heart failure. Moderate to severe MR occurs in up to 19% of patients after myocardial infarction and 15% of patients with dilated cardiomyopathy. Ischemic MR is a growing clinical problem. It is associated with a poor prognosis, doubling mortality after myocardial infarction at 5 years. Increased mortality is independent of the severity of ventricular dysfunction but related to the degree of MR, with a graded relationship between severity and reduced survival, even in patients with mild to moderate MR. According to Carpentier classification, the mechanism of valvular regurgitation can be classified based on leaflet dysfunction to provide a practical framework for the evaluation of different approaches.

It is widely accepted that surgical valve repair, when feasible, is the optimal treatment in patients with severe MR. However, surgery for functional ischemic MR remains a challenge. Operative mortality is higher than in organic MR, and long-term prognosis is less satisfactory with a higher recurrence rate of MR after valve repair. Surgery on the regurgitant mitral valve should not be considered in severely ill patients with low output, severe right ventricular failure, and significant comorbidities. A large proportion of patients with both degenerative and functional MR are poor candidates for surgery, most often due to associated poor left ventricular function or advanced age.

The past 5 years have seen the introduction into the preclinical arena of several types of devices for potential treatment of functional and ischemic MR by a percutaneous approach. Despite several concerns about the position of the CS above the MVA and the risk of crossing of the left circumflex artery, initial results are very encouraging. Perhaps, it may be explained in part by the fact the mitral MVA is a band-like fibrous tissue rather than a more rigid ring structure. This may allow for the correction of MR by reshaping of the annulus with left atrial traction rather than direct compression of the MVA.

Webb et al have reported on initial human experience with a percutaneous transvenous mitral annuloplasty system called Viking (Viking, Edwards Lifesciences Inc). The percutaneous transvenous mitral annuloplasty system consists of a 12F outer-diameter guide catheter and dilator, a 9F delivery catheter, and a nickel-titanium alloy (nitinol) implant. The implant itself is made up of 3 sections: a distal self-expanding anchor, a spring like “bridge,” and a proximal self-expanding anchor.

The distal anchor is deployed in the great cardiac vein, and the proximal anchor is deployed in the proximal CS. The bridge has shape-memory properties and a biodegradable substance that result in shortening forces at body temperature over time. The anchors draw the proximal CS and distal great cardiac vein together, whereas the bridge section tenses and straightens, indirectly displacing the posterior annulus anteriorly and reducing mitral annulus diameter and septal-lateral distance. This device was successfully implanted in 4 of 5 patients studied in the feasibility trial. In one patient, the device could not be advanced fully into the CS because of difficulty in obtaining coaxial guide position. A second patient developed transient atrial fibrillation during cannulation of the CS. The principal complication of this technique was a separation of the nitinol bridge segment, which was documented in 3 of 4 patients who had received implants. The separation was noted on follow-up chest radiographs at 22, 28, and 81 days. Migration of the anchors was not observed. Although there were no adverse clinical events associated with device separation, feasibility study enrolment was discontinued. Later, the device was modified and the preliminary results of the safety trial on the MONARC system were presented during TCT 2007 and will be published. Additional device separations were noted. Also, because tension on the mitral annulus and periannular tissue occurs by bridge shortening and is not under operator control, late compression of the circumflex artery was reported and remains a safety concern with this technique.

One of the most advanced devices designed for transvenous mitral annuloplasty currently undergoing clinical testing is the CARILLON Mitral Contour System (Cardiac Dimensions Inc,
Kirkland, Wash). The device is designed to be introduced into the coronary venous system by a dedicated delivery catheter. It is composed of 2 nitinol and titanium anchors designed to be fixed within the lumen of the coronary veins and connected by a curved nitinol bridge. After deployment of the distal anchor in the great cardiac vein, tension is applied by pulling the system and then the proximal anchor is deployed within the CS. Thus, full control of the tension by the operator is possible and the risk of permanently compromising the circumflex artery is eliminated as the device could be recaptured, if necessary.

The procedure is performed via the right internal jugular venous approach. A proprietary 9F delivery catheter is introduced deeply into the CS and great cardiac vein over a guidewire (Terumo) and over a 7F multipurpose catheter (Figure 4A and 4B). Coronary venography is performed through the delivery catheter with a calibration catheter in place (Figures 4D and 5A). This allows precise measurement of the length and diameters of the great cardiac vein and the CS. After selecting the appropriate size CARILLON implant, the device is introduced into the coronary venous system (Figure 5B) and the distal anchor is deployed. After verifying that the deployed distal anchor does not compromise the circumflex coronary artery, tension is applied by pulling the whole system to plicate perianular tissue and deflect the posterior leaflet toward the anterior leaflet of the mitral valve. Coronary angiography is repeated for safety. Next, the proximal anchor is deployed (Figure 5C) in the CS and the effect of the implanted system on the degree of MR is verified by echocardiography (Figure 6). If found to be safe and effective, the implant is released from the delivery system (Figure 5D). At any time before release, the implant can be recaptured and an additional implant attempt can be made if desired.

The CARILLON system, after extensive preclinical testing, has been introduced into clinical studies and has been evaluated in a multicenter clinical trial AMADEUS. The trial has been completed and percutaneous mitral annuloplasty in patients with MR and dilated cardiomyopathy resulted in acute MR reduction (grade 3.0 ± 0.6 to 2.0 ± 0.8, P < 0.0001) and permanent implantation in 30 out of 43 attempts. Additional measurements in 20 implanted patients showed reductions in vena contracta (0.69 ± 0.29 to 0.46 ± 0.26 cm, P < 0.0001), effective regurgitant orifice area (0.33 ± 0.17 to 0.19 ± 0.08 cm², P < 0.005), regurgitant volume (40 ± 20 to 24 ± 11 mL, P = 0.01), and jet area/leaf atrial area (45 ± 13% to 32 ± 12%, P < 0.0005). Coronary arteries were crossed in 36 patients (84%). Arterial compromise contributed to lack of implantation in 6 patients (14%). Core laboratory data on the chronic safety and efficacy endpoints are pending.

**Future Directions**

Although transvenous interventional techniques have not yet been widely adopted for routine use, coronary venous catheterization opens new horizons for interventional cardiology. Rapid development of both percutaneous as well as cardiac surgical revascularization techniques makes trans-coronary-venous therapies for refractory ischemia less useful in clinical practice. Their future may be in providing solutions for “no-option” patients.

The potential value of skeletal myoblast transplantation for the reduction of ischemic MR has been recently suggested by Messas et al. The trans-coronary-venous approach might be an interesting alternative for cell injections in these patients, especially that the technique allows repeated safe cell injections. In addition, the technique may be used for intramyocardial injec-
tion of drugs and for gene therapies, if proven for effective treatment of "no option" patients.

The role for percutaneous transvenous mitral annuloplasty, given current surgical techniques, remains to be seen. Recently, an expert panel defined the rules for evaluation of percutaneous techniques for valve repair.62 Future trials should include comparison of percutaneous mitral valve repair to optimal medical therapy in nonsurgical candidates with either end-stage cardiomyopathy or type IIIb severe MR or elderly patients with significant comorbidities and type II dysfunction. Comparison should be made to open surgical mitral valve repair in patients with types I, II, and IIIb dysfunction. Moreover, the use of this technique in the early stage of postinfarction MR may be considered. Beeri et al78 have shown in an ovine model of ischemic MR, that early correction attenuates the processes of left ventricular remodeling. Thus, percutaneous valve therapies for functional MR may not only provide acute hemodynamic improvement but also inhibit the progression of ventricular dilatation.

Rapid development of trans-coronary-venous interventional techniques will require additional training among interventional cardiologists as well as more knowledge on venous anatomy and the mechanical properties of coronary veins.

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Disclosures
None.

Figure 5. Procedural steps of percutaneous mitral valvuloplasty using Carillon system—venous calibration and implantation of the device. A, 9F guiding catheter was introduced into coronary venous system over the diagnostic catheter, which was later replaced with a calibration catheter, having 1 cm marks (arrows) and coronary venography was performed in RAO 30 projection allowing assessment of the vein length; B, implantation of the distal anchor (arrow) in LAO 30 CAUD 20 view; C, implantation of the proximal anchor (arrow); D, after assessment of coronary arteries and transesophageal echocardiography for evaluation the efficacy, the device is released. Coronary angiography in RAO 35 CAUD 20 after device implantation shows normal flow in the circumflex artery despite crossing the artery with the device within vein (arrow).

Figure 6. Example of transesophageal echocardiography before (A) and immediately after (B) trans-coronary-venous mitral annuloplasty with the Carillon device. Note the marked reduction of the massive MR jet.
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