Exploring a New Systematic Route for Left Ventricular Pacing in Cardiac Resynchronization Therapy

Frédéric Anselme, Mohammad Albatat, Christelle Marquié, Christophe Leclercq, Philippe Ritter, Jean-François Ollivier, Nicolas Shan, Filippo Ziglio, Delphine Feuerstein

Circulation Journal
Circ J 2021; 85: 283–290
doi:10.1253/circj.CJ-20-0266

ORIGINAL ARTICLE
Devices

Exploring a New Systematic Route for Left Ventricular Pacing in Cardiac Resynchronization Therapy

Frédéric Anselme, MD, PhD; Mohammad Albatat, BSc; Christelle Marquié, MD; Christophe Leclercq, MD, PhD; Philippe Ritter, MD; Jean-François Ollivier, BSc; Nicolas Shan, BSc; Filippo Ziglio, BSc; Delphine Feuerstein, PhD

Background: Frequency and distribution of left ventricular (LV) venous collaterals were studied in vivo to evaluate the ease and feasibility of implanting a new ultra-thin LV quadripolar microlead for cardiac resynchronization therapy (CRT).

Methods and Results: Evaluable venograms were analyzed to define the prevalence of venous collaterals (>0.5 mm diameter) between: (1) different LV segments; and (2) different major LV veins in: unselected patients who underwent CRT from 2008 to 2012 at Rouen Hospital, France (retrospective); and CRT patients from the Axone Acute pilot study in 2018 (prospective). In prospective patients with evaluable venograms, LV microlead implantation was attempted. Thirty-six (21/65 retrospective, 15/20 prospective) patients had evaluable venograms with ≥1 visible venous collaterals. Collaterals were found between LV veins in all CRT patients with evaluable venograms. Regionally, prevalence was highest between: the apical inferior and apical lateral (42%); and mid inferior and mid inferolateral (42%) segments. Collateral connections were most prevalent between: the inferior interventricular vein (IIV) and lateral vein (64% [23/36]); and IIV and infero-lateral vein (36% [13/36]). Cross-vein microlead implantation was possible in 18 patients (90%), and single-vein implantation was conducted in the other 2 patients (10%).

Conclusions: Venous collaterals were found in vivo between LV veins in all CRT patients with evaluable venograms, making this network an option for accessing multiple LV sites using a single LV microlead.

Key Words: Cardiac resynchronization therapy; Coronary sinus angiogram; Left ventricular lead; Multisite pacing; Venous collateral

Left ventricular (LV) lead position is an important determinant of how heart failure (HF) patients respond to cardiac resynchronization therapy (CRT).[1] Multipoint pacing, LV pacing with 2 of 4 bipoles of a quadripolar lead at 1 LV site, is a significant advance in CRT that has the potential to improve the response of HF patients to CRT, especially those with fibrotic or scarred myocardium.[2,3]

By increasing the velocity of impulse propagation and decreasing LV activation time,[4] multipoint pacing is capable of addressing the problems of impaired conduction and heterogeneous ventricular depolarization. Limitations do, however, exist and these include faster battery depletion and the inability to completely avoid stimulation-related problems, such as high-pacing thresholds, failure to capture heart cells and phrenic nerve stimulation.

Pacing the LV at 2 different sites (i.e., multisite pacing) may be even more effective than multipoint pacing at overcoming the conduction- and depolarization-related problems mentioned above. However, despite largely positive findings, the need for 2 coronary sinus leads means complications linked to implantation are more likely,[4] lead-associated problems are more common,[5] and lead impedance may decrease with the suboptimal electronic configuration. Furthermore, some patients do not have 2 accessible LV veins for 2 coronary sinus leads.[6]

A possible solution to these limitations is to use a single ultra-thin LV microlead that is able to pass from one large LV vein into another using the venous collateral (aka "venous anastomosis") network as a "bridge". Over the last decade, a collateral approach has been sporadically-but-successfully used to implant LV leads.[7–12]

An important limitation to the systematic use of the venous collateral network is that the cardiac venous microcirculation in humans is still poorly understood[13,14] and is even now the subject of basic research.[15] Anatomically, the existence of the venous collateral network has been known about for many years thanks to corrosion casting,[16] but

Received June 8, 2020; revised manuscript received October 9, 2020; accepted November 15, 2020; J-STAGE Advance Publication released online January 27, 2021 Time for primary review: 11 days

Rouen University Hospital, Rouen (F.A.), France; Oslo University Hospital, Oslo (M.A.), Norway; Lille University Hospital, Lille (C.M.); Rennes University Hospital, Rennes (C.L.); Bordeaux University Hospital, Pessac (P.R.); and MicroPort CRM, Clamart (J.-F.O., N.S., F.Z., D.F.), France

Mailing address: Frédéric Anselme, MD, PhD, Service Cardiologie CHU, 1 Rue De Germont, 76000 Rouen, France. E-mail: frederic.anselme@chu-rouen.fr

ISSN-1346-9843

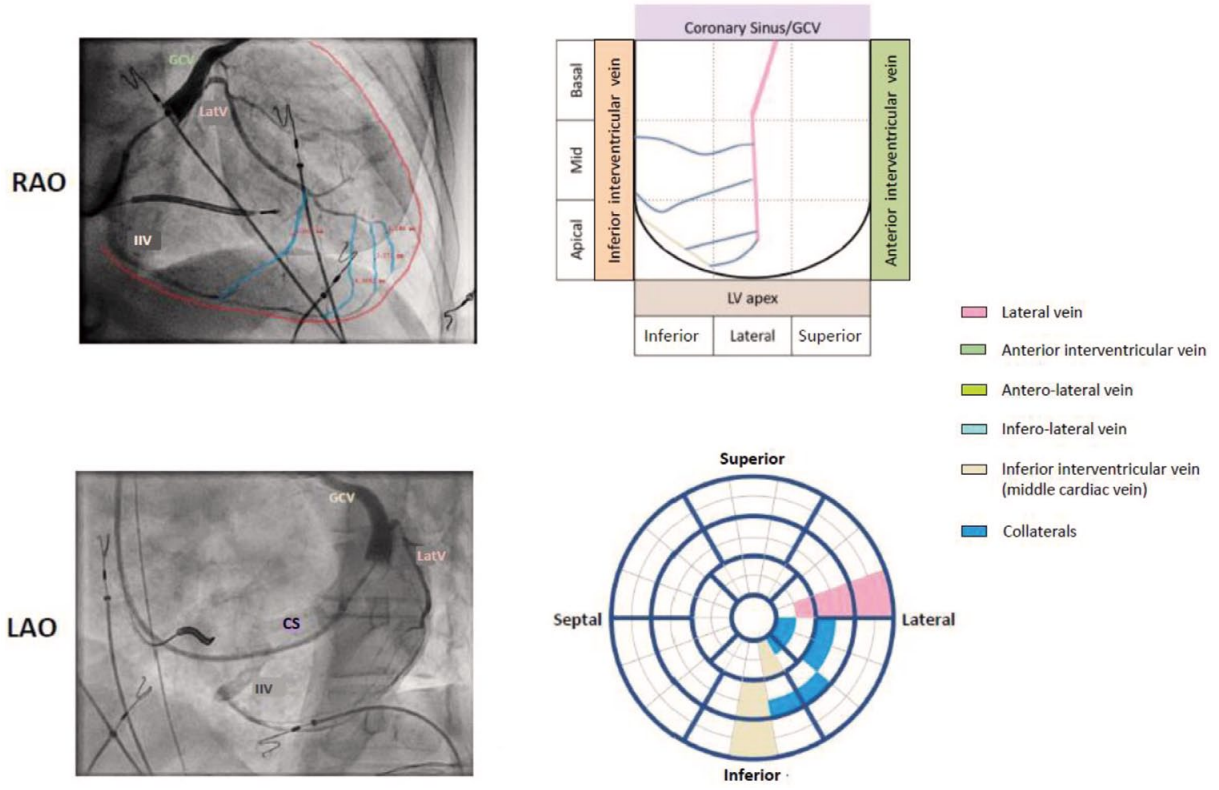


Figure 1. X-ray images showing LV venous network next to corresponding 17-segment bullseye and 3×3 grid representations of the LV. CS, coronary sinus; GCV, great cardiac vein; LAO, left anterior oblique; LatV, lateral vein; LV, left ventricle; IIV, inferior interventricular vein (middle cardiac vein); RAO, right anterior oblique.

little has been documented in living subjects about the frequency or distribution of venous collaterals in the LV. The systematic analysis of the LV venous collateral network at implantation may offer a valuable alternative to current standard practice for personalizing the approach to LV lead placement.

The aim of this study was to explore the ease and feasibility of implanting an ultra-thin LV quadripolar microlead by studying the anatomic frequency and distribution of venous collaterals in vivo.

Methods

Study Design

The venous collaterals study consists of a retrospective analysis of venograms from Rouen Hospital in France and also of a prospective analysis of the venograms of CRT patients from the Axone Acute pilot study (ClinicalTrials.gov identifier NCT03750058).

Retrospective Analysis From Rouen Venograms Usable venograms, with good occlusion (determined by the absence of leakage of contrast agent during the venogram) and identifiable collaterals (obtained by using an adequate amount and pressure of contrast agent to produce a high-quality image of the proximal LV circulation), of unselected patients who underwent CRT between 2008 and 2012 at Rouen Hospital were analyzed to define the prevalence and location of venous collaterals in the LVs of living patients. Only collaterals >0.5 mm in diameter (estimated using the diameter of a pacing lead observed in the same image) were considered.

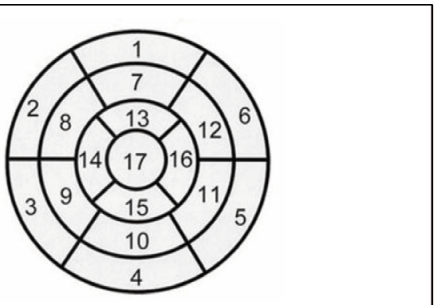
Axone Acute Study Design Axone Acute (Acute assessment of a micro multipolar lead for enhanced CRT) was an open prospective, single-arm multicenter pilot study designed to characterize the acute performance, including lead implant efficiency and safety, of an ultra-thin LV microlead temporarily implanted during a scheduled CRT implant procedure. Microlead testing, including implantation, lasted 20 min maximum. Adult patients from hospitals in Lille, Rouen, Bordeaux and Rennes in France with an indication for a primary implant (including upgrade to CRT-P or -D), according to the 2016 European Society of Cardiology (ESC) HF guidelines, were included from August to November 2018.[17] Previous failure of coronary sinus catheterization or LV lead implantation was an exclusion criterion. The venograms of patients with adequate balloon occlusion (absence of leakage of contrast agent during the venogram) and sufficient adequate view angles were analyzed to determine the prevalence and location of venous collaterals in the LV, as for the retrospective analysis patients. Axone Acute complied with Good Clinical Practice described in ISO 14155 and with the principles set forth in the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study. Ethical committee approval was obtained from all the institutions involved.

Device Description

The quadripolar ultra-thin LV microlead used in the Axone Acute pilot study (Axone 4LV microlead; MicroPort CRM, Clamart, France) is a 1.2 Fr (0.4 mm) pacing microlead with an IS4 connector designed for LV stimulation through the coronary vein network (**Supplementary Figure 1**). The high-impedance microlead has 4 electrodes with a small surface area (0.6 mm^2 per electrode) to enable multisite pacing. Total lead length is ~100 cm, with electrodes (LV1–LV4) spaced from 62 mm to 160 mm, depending on model size. The LV microlead is lumenless and requires a specially designed micro-catheter (Axone μGuide catheter; MicroPort CRM), with a proximal diameter of 3.9 Fr (1.3 mm) and a distal diameter of 2.4 Fr (0.8 mm), for implantation. The LV microlead is not yet commercially available.

Image Analysis

The principal method for determining the LV myocardial segments connected by venous collaterals was the manual projection of venograms onto a 17-segment circumferential polar plot of the LV ("bullseye" representation) described in a scientific statement from the American Heart Association in 2002 (**Figure 1** and **Supplementary Appendices 1**,**2**).[18] Right anterior oblique (RAO) views were used to determine the vertical position of veins, and left anterior oblique (LAO) or anterior-posterior (AP) views were used to determine their horizontal position. An alternative-but-complementary representation on a 3×3 grid was also used to depict the location of coronary sinus veins and venous collaterals.[19] The grid is composed of 3 vertical sections (basal, mid and apical) and 3 horizontal sections (inferior, lateral and superior); for reference, the relative positions of key LV cardiac structures are also displayed (**Figure 1** and **Supplementary Appendices 3**,**4**).[20]



1. Basal superior
2. Basal superoseptal
3. Basal inferoseptal
4. Basal inferior
5. Basal inferolateral
6. Basal superolateral
7. Mid superior
8. Mid superoseptal
9. Mid inferoseptal
10. Mid inferior
11. Mid inferolateral
12. Mid superolateral
13. Apical superior
14. Apical septal
15. Apical inferior
16. Apical lateral
17. Apex

Connected segments	Prevalence
15-16	15 (42%)
10-11	15 (42%)
11-12	12 (33%)
11-15	8 (22%)
13-15	6 (17%)
12-15	5 (14%)
7-12	4 (11%)
10-12	4 (11%)
1-6	2 (6%)
13-16	2 (6%)
4-6	2 (6%)
5-6, 11-16, 12-16	1 (3%)

Figure 2. Prevalence of venous collaterals between connected left ventricular segments in a 17-segment circumferential polar plot ("bullseye" representation) in the overall population.

Study Endpoints

Existence/Position of Venous Collaterals The primary endpoint was the prevalence of venous collaterals between connected LV segments based on a 17-segment circumferential polar plot ("bullseye" representation) model.[18] Secondary endpoints included: venous collateral density in the different LV segments of a 17-segment bullseye representation; the occurrence and prevalence of venous collaterals between connected LV segments based on a 3×3 grid model of the LV;[19] and the prevalence and occurrence of venous collaterals between major LV veins that are coronary sinus tributaries of the greater cardiac vascular system and typically located in the LV wall. For this last endpoint, the naming of veins was based on the origin of the vein; that is, inferior interventricular, infero-lateral, lateral, antero-lateral or anterior interventricular, at the base of the ventricle.

Implantation Success Rate With the LV Microlead The rate of successful LV microlead implantations was measured in Axone Acute patients in whom implantation was attempted. To implant the LV microlead (**Supplementary Figure 2**), a guidewire was first inserted into position in the LV venous coronary circulation. The Axone μGuide catheter was next passed over the guidewire, which was then withdrawn so the LV microlead could be inserted through the catheter. Lastly, the catheter was pulled back to expose the electrodes of the LV microlead, and locked in place at the connector. Cross-vein implantation was prioritized over single-vein implantation, where feasible. "Cross-vein implantation" was the implantation of the LV microlead in 2 different LV veins, by the passage of the LV microlead from one LV vein into another LV vein via a venous collateral (**Supplementary Figure 3**). The time taken for implantation of the LV microlead (cross-vein and single-vein) was evaluated.

Safety of Implantation With the LV Microlead Adverse events (AEs) and serious AEs (SAEs) related to the Axone Acute study protocol; that is, the LV microlead and its implantation, were reported. Adverse device effects were also investigated. The safety of the LV microlead was evaluated 1 month after the implant testing procedure.

Statistical Methodology

In the Axone Acute pilot study, the sample size estimation of 25 enrolled patients was based on a non-testing rate for the LV microlead in 20% and a minimum of 20 evaluable patients. Safety was analyzed in all evaluable patients; that is, patients in whom LV microlead testing was initiated, regardless of whether testing was completed. Summary statistics are provided for AEs, SAEs and adverse device effects. Statistical analysis was performed by the Biostatistics Department of Rouen University Hospital, France.

Results

Populations

Of the 65 patients from the Rouen retrospective analysis, adequate venograms with visible venous collaterals were

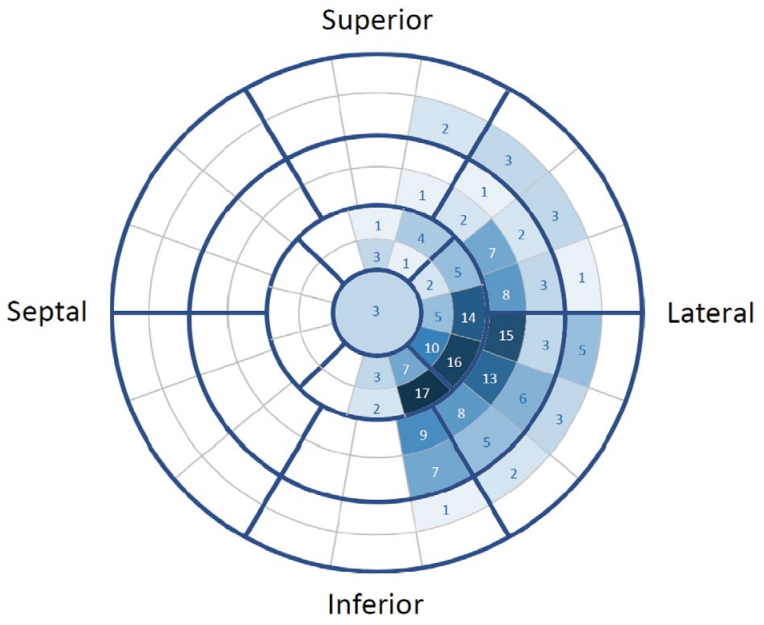


Figure 3. Bullseye representation of venous collateral density in the left ventricle in the overall population. Numbers in the sub-segments represent the number of times a venous collateral was detected in each sub-segment.

Table 1. Prevalence of Connections Between the Main LV Veins in the Overall Population (n=36)

	IIV	ILV	LatV	ALV	AIV
IIV	0	13 (36)	23 (64)	5 (14)	6 (17)
ILV	0	0	11 (31)	4 (11)	1 (3)
LatV	0	0	0	2 (6)	5 (14)
ALV	0	0	0	0	None*
AIV	0	0	0	0	0

Data are presented as n (%). AIV, anterointerventricular vein; ALV, anterolateral vein; LatV, lateral vein; LV, left ventricular; IIV, inferior interventricular vein (middle cardiac vein); ILV, infero-lateral vein. *Venous collaterals could not be identified with certainty.

obtained in approximately one-third (n=21 [32%]) (**Supplementary Figure 4**). Venous collaterals were not visible in many patients either because of poor occlusion and consequent inadequate dissipation of contrast agent (n=27 [42%]) or because collaterals could not be identified due to the 2-D nature of the images or inadequate amount and/or pressure of the contrast agent (n=17 [26%]).

In the Axone Acute pilot study, 24 patients were enrolled and an implant of an LV microlead was attempted in 20 (**Supplementary Figure 4**). Four patients were excluded (problem of venous access [n=2], coronary sinus dissection [n=1], and difficult coronary sinus anatomy [n=1]). Of the 20 patients included, 15 patients had legible venograms and 5 patients did not (insufficient viewing angles available [n=3], inadequate balloon occlusion [n=1], and no venogram [n=1]). Of the 15 patients, 11 had ≥2 X-ray views (RAO only [n=2], AP only [n=2]).

Patients from the Rouen retrospective cohort and Axone Acute pilot study were about the same age (67.0±13.5 vs. 66.4±11.1 years), but Rouen patients were less likely to be overweight (BMI 25.0±2.8 vs. 29.3±6.0 kg/m^2) (**Supplementary Table 1**). Moderate-to-severe symptomatic HF (New York Heart Association class III/IV) was more common in Rouen patients (52% vs. 33%), which was reflected by a lower mean LV ejection fraction (24.0±6.6% vs. 30.9±8.5%). In both groups, most patients (81% Rouen vs. 80% Axone Acute) had an indication for CRT-defibrillator. Half (48%) of Rouen patients had rhythm disorders compared with one-quarter (27%) of Axone Acute patients. All patients in both groups had a conduction disorder and cardiomyopathy, but valvular heart disease was less common in Rouen patients (14% vs. 60%). Frequent comorbidities in both groups included dyslipidemia (70% Rouen vs. 73% Axone Acute) and hypertension (55% vs. 60%). The majority of patients were on multiple cardiovascular medications, including an angiotensin receptor-neprilysin inhibitor (ARNI) or renin-angiotensin-aldosterone system (RAAS) inhibitor (90% Rouen vs. 100% Axone Acute), β-blockers (80% vs. 93%) and diuretics, excluding spironolactone (80% vs. 60%).

Existence/Position of Venous Collaterals

Overall Analysis Venous collaterals were generally most prevalent between adjacent connected segments at a mid or apical level in the lateral and inferolateral regions of the LV. The prevalence of collaterals was highest between: the apical lateral and apical inferior (42%); mid inferolateral and mid inferior (42%); and mid superolateral and mid inferolateral (33%) segments (**Figure 2**).

In the 3×3 grid representation of the LV, the prevalence

Table 2. Occurrence of Venous Collaterals Between the Main LV Veins in the Overall Population

	IIV	ILV	LatV	ALV	AIV
IIV	–	19 (17)	48 (44)	6 (6)	7 (6)
ILV	–	–	14 (13)	5 (5)	1 (1)
LatV	–	–	–	3 (3)	6 (6)
ALV	–	–	–	–	None*
AIV	–	–	–	–	–

Data are presented as n (%). Abbreviations as in Table 1. *Venous collaterals could not be identified with certainty.

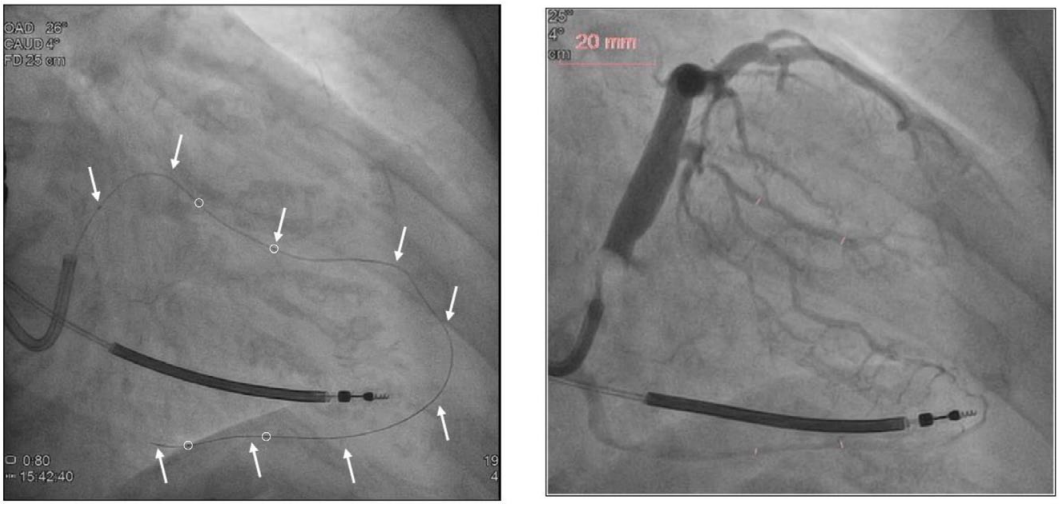


Figure 4. Example of an X-ray and corresponding venogram for a patient with a left ventricular microlead in situ. The position of the microlead is indicated by white arrows and the position of electrodes by white circles.

of collateral connections was greatest between the mid inferior and mid lateral segments and between the apical inferior and apical lateral segments, with connections found in 25 (69%) and 23 (64%) patients, respectively. Venous collaterals also occurred most frequently between these same sets of segments, with 36 (35%) collaterals detected between the mid inferior and mid lateral segments, and 32 (31%) collaterals detected between the apical inferior and apical lateral segments (**Supplementary Table 2** and **Supplementary Figure 5**).

Venous collaterals were found throughout the LV in living CRT patients, most commonly connecting major LV veins on the lateral side of the LV (**Figure 3**). The highest density of mid-to-large diameter (>0.5 mm) venous collaterals in the LV was in the mid and apical inferolateral segments, with a higher density in the apical region in Rouen patients and a higher density in the mid region in Axone Acute patients (**Supplementary Figure 6**).

On average, 2 collateral connections per patient were found between different major LV veins, with 70 distinct intervein connections found in the 36 patients analyzed. The most prevalent connections were between the inferior interventricular vein (IIV) and lateral vein (LatV) in 64% of patients, IIV and infero-lateral vein (ILV) in 36% of patients, and ILV and LatV in 31% of patients (**Table 1**). With 109 collaterals found in 36 patients, there were on average 3 mid-to-large diameter venous collaterals detected per patient. Collaterals occurred most frequently between the IIV and LatV (44%), IIV and ILV (17%), and ILV and LatV (13%) (**Table 2**). The vein with the most venous collateral connections was the IIV, with 80 (73%) collaterals. Collateral location only indicates where 2 LV veins are interconnected. During implantation, the LV microlead is threaded through and past the collateral and, with the right degree of separation between the2 electrode pairs, pacing is possible at any point within the 2 LV veins.

Venous Collateral Access/Implantation

Axone Acute Analysis A LV microlead was successfully implanted in all 20 CRT patients in whom implantation was attempted. Cross-vein implantation of the LV microlead was possible in most (n=18 [90%]), and single-vein implantation possible for the remainder (n=2 [10%]) (**Figure 4**). Mean time for the cross-vein placement of the micro-catheter was 5.2±6.1 min, and mean time for LV microlead cross-vein placement was 2.4±2.5 min. Mean time for LV microlead single-vein placement was 4.6±7.0 min. Mean total protocol-related fluoroscopic time in 20 patients was 5.2±2.9 min. Pacing capture threshold (PCT) was tested in all cases and was obtained in 19/20 patients (95%), for a mean PCT of 1.99±2.05 V (median 1.1V) at 0.5 ms. The associated pacing impedance was 1,818±376 Ohms. In addition, because of its high impedance profile, the PCT of the LV microlead is equivalent in energy to the PCT of a standard LV lead.

Axone Acute Safety Five AEs and 5 SAEs were reported

in 10 different patients. None of the AEs were related to the Axone Acute protocol; that is, to the LV microlead or to its implantation. Of the 5 SAEs, 4 SAEs were unrelated to the Axone Acute protocol and 1 SAE (patient hospitalized for palpitations with atrial fibrillation on electrocardiogram) was categorized as "unknown" and may have been related to the protocol. No adverse device effect was observed. A detailed list of these AEs is presented in **Supplementary Table 3**.

Discussion

The existence of venous collaterals interconnecting major LV veins in all CRT patients for whom evaluable venograms were available was confirmed in vivo by this study. Mid-to-large diameter (>0.5 mm) venous collaterals were located throughout the LV, but were most commonly found interconnecting major LV veins on the lateral side of the LV. The highest density of venous collaterals was in the mid and apical inferolateral segments of the LV. Systematic access to the venous collateral network with an ultra-thin LV microlead, with a diameter 3× to 4× smaller than that of conventional LV leads, appears feasible and safe. Cross-vein implantation with an LV microlead was successful in most patients in whom this procedure was attempted.

Venous Collaterals and the Cardiac Venous System

Previous ex vivo research in humans has shown that venous collaterals are so common in the cardiac venous circulation that some investigators regard this network to be a venous plexus.[14] Their proven abundance meant we were able to find in vivo an average of 2 different LV intervein connections per patient and 3 venous collaterals per patient. We noted mid-to-large venous collaterals to be most dense in the apical region, which is where the highest density of venous collaterals has been observed elsewhere.[14] In fact, we were able to ascertain more precisely in our population that venous collaterals with a diameter >0.5 mm were most dense at the bottom of the apex, next to the mid section, rather than at the tip of the apex. An old anatomical study in humans found that large venous collaterals (diameter >1 mm) were present in the apical region in nearly all subjects (97%).[21]

Some former research has indicated cardiac veins may be connected to extracardiac vessels, like the vasa vasorum or mediastinal veins, as well as the macroscopic existence of arteriovenous collaterals, but there were no indications from our in vivo observations to confirm either of these past findings.[14]

When LV venous collaterals were prospectively sought, the data of fewer patients were lost due to inadequate balloon occlusion (5% [1/20] Axone Acute vs. 42% [27/65] Rouen) and insufficient views/unidentifiable collaterals (20% [4/20] Axone Acute vs. 26% [17/65] Rouen) (**Supplementary Figure 4**).

Reporting cardiac anatomical findings is currently made more complicated by the existence of 2 descriptive systems, anatomical position and Valentine position.[22] The systematic use of a single, attitudinally appropriate descriptive system could, in future, help avoid confusion and aid researchers and clinicians to more easily understand new developments in cardiac therapy.[23]

Potential Effect of Technological Developments of LV Leads

Response to CRT currently has a 70% success rate, which the medical community is constantly seeking to enhance. The use of an extra LV lead to offer the possibility of multisite pacing may increase response to therapy vs. conventional CRT, but not potentially without cost or complication: increased risk of lead-related complications,[5] insufficient accessible veins,[6] and increased power consumption due to the suboptimal electronic configuration. LV microleads are a way of delivering multisite pacing without some of these downsides; vein access and suboptimal electronic configuration might be less of a problem, although further research is needed to elucidate the risk of lead-related complications with a LV microlead vs. a standard LV lead.

In addition, cross-vein implantation of an LV microlead offers a wider variety of pacing vectors compared to single-vein implantation of a standard quadripolar lead; in the case of suboptimal- or non-response, a completely different site to that which was initially targeted can be stimulated. From a research perspective, this new LV microlead may also help us elucidate mechanisms underlying why CRT is successful in some HF patients and a failure in others.

Improved understanding of cardiac venous anatomy will be required to take advantage of upcoming technological advances in CRT.[24] For optimal efficacy, CRT relies on the correct positioning of the LV lead in the appropriate zone affected by delayed electrical activation and mechanical dyssynchrony; for each patient, dyssynchrony varies in terms of location, size and degree.[19,25,26] Without proper consideration of these factors, lead positioning is likely to be suboptimal.[27]

LV microleads have several potential benefits: (1) systematic access of venous collaterals during lead implantation; (2) better flexibility, allowing better navigation of acute angles and tortuosity in smaller veins; (3) better distal reach via access to smaller veins; and (4) enhanced myocardial penetration, as collateral width decreases towards the endocardium.[21] Any or all of these possibilities could improve LV lead positioning and thus help optimize CRT.

It remains to be seen in the long term whether reduced LV lead width is associated or not with increased lead fragility or an increase in implant- or lead-related AEs. If long-term studies exclude these concerns and confirm the positive findings of our study, then LV microleads could become a valuable tool for extending access to new pacing sites in the LV. In addition to LV microleads, other technologies to improve CRT response such as wireless LV stimulation and His bundle pacing are also currently being investigated and developed.[28]

Study Limitations

The retrospective nature of the examination of Rouen patients meant that a substantial amount of critical data were missing, leading to the subsequent exclusion of many of these patients from further analyses. This, in turn, meant that the sample size analyzed was relatively small. The findings should thus be considered exploratory and interpreted with care. They do, nevertheless, shed new light on the venous collateral network, its investigation in vivo, and its potential in CRT for accessing different LV sites. A lack of venogram clarity and of appropriate angiographic projections were important limitations leading to loss of data. Lack of venogram clarity was caused, for instance, by inadequate balloon occlusion causing leak back of con-

trast agent. Inadequate angiographic projections made it impossible to locate and/or confirm the presence of LV veins and venous collaterals. For instance, the presence of septal collaterals could not be confirmed because of the unavailability of RAO and AP views to identify whether the IIV and anterointerventricular vein (AIV) were connected or whether they just crossed. Detection of venous collaterals between veins distal to the coronary sinus was suboptimal. The anterolateral vein (ALV) and AIV were on the edge of RAO venograms making it difficult to observe connections and, in 2-D RAO or AP venograms, the AIV can lie close to or on top of the ALV. Their distal location meant they were last to receive contrast agent and required the longest exposure time. Lastly, mapping of collateral density ignored smaller diameter vessels (<0.5 mm).

Conclusions

Venous collaterals were found in vivo between LV veins in all CRT patients for whom evaluable venograms were available. Collaterals with a diameter >0.5 mm were widespread throughout the LV, but most commonly found in the apical region interconnecting major LV veins on the lateral side, with high densities of venous collaterals at the border of the LV mid and apical inferolateral segments. Cross-vein implantation of the LV microlead was possible in most CRT patients with evaluable venograms (90%), with single-vein implantation feasible in the rest (10%). This innovative CRT delivery solution based on the use of a single micro-catheter-guided LV microlead to access multiple LV sites via the venous collateral network has the potential to extend current CRT pacing options.

Acknowledgments

The authors would like to thank: Dr André Gillibert, MD, for his statistical expertise; Anaïs Balland, MSc, for her help in data acquisition and analysis; and Anne Rousseau-Plasse, PhD, and John Plant, BPharm, for their medical writing and editing support.

Sources of Funding

The Axone Acute pilot study was funded by MicroPort CRM and the European Union (H2020-FTI [Fast Track to Innovation] Pilot-2016, grant agreement no. 737817; H2020 MSCA [Marie Skłodowska-Curie Actions] ITN [Innovative Training Network] program for the WiBEC [Wireless In-body Environment Communication] project, grant agreement no. 675353).

Disclosures

F.A. is a consultant for MicroPort CRM, Medtronic and Boston Scientific. C.M. has received fees from MicroPort CRM for scientific research and Board participation. C.L. has worked as a consultant for and received speaker fees from MicroPort CRM, Medtronic, Biotronik, Abbott and Pfizer. P.R. is a speaker and consultant for MicroPort CRM and a speaker for Medtronic. J.-F.O., N.S., F.Z. and D.F. are all employees of MicroPort CRM.

IRB Information

Name of the ethics committee: Comité de Protection des Personnes (CPP) Ile de France II (reference number: 2017-A02803-50).

Data Availability

Individual participant data underlying the results are available in the supplementary material file corresponding to this publication (see **Supplementary Appendices**). These data will be available immediately following publication of the article to anyone who wishes to access them. Additional information about data availability can be found in the data sharing statement below:

Data Sharing Statement

1. Will the individual deidentified participant data (including data dictionaries) be shared?
→ Yes.
2. What data in particular will be shared?
→ Bullseye representations and 3×3 grid representations of the LV distribution of coronary sinus veins and venous collaterals in these CRT patients.
3. Will any additional, related documents be available? If so, what are they? (e.g., study protocol, statistical analysis plan, etc.)
→ No additional, related documents will be made available.
4. When will the data become available and for how long?
→ These data will be available immediately following publication of the article for the duration of publication.
5. By what access criteria will the data be shared (including with whom)?
→ These data are available in the **Supplementary Files** submitted alongside the main manuscript and are therefore accessible to anyone who wishes to access them.
6. For what types of analyses, and by what mechanism will the data be available?
→ There is no restriction on the type of analyses for which these data can be used. These data are available in the **Supplementary File** submitted with the manuscript.

References

1. Khan FZ, Virdee MS, Fynn SP, Dutka DP. Left ventricular lead placement in cardiac resynchronization therapy: Where and how? *Europace* 2009; **11:** 554–561.
2. van Everdingen WM, Cramer MJ, Doevendans PA, Meine M. Quadripolar leads in cardiac resynchronization therapy. *JACC Clin Electrophysiol* 2015; **1:** 225–237.
3. Siciliano M, Migliore F, Badano L, Bertaglia E, Pedrizzetti G, Cavedon S, et al. Cardiac resynchronization therapy by multipoint pacing improves response of left ventricular mechanics and fluid dynamics: A three-dimensional and particle image velocimetry echo study. *Europace* 2017; **19:** 1833–1840.
4. Thomas G, Kim J, Lerman BB. Improving cardiac resynchronisation therapy. *Arrhythm Electrophysiol Rev* 2019; **8:** 220–227.
5. Behar JM, Bostock J, Ginks M, Jackson T, Sohal M, Claridge S, et al. Limitations of chronic delivery of multi-vein left ventricular stimulation for cardiac resynchronization therapy. *J Interv Card Electrophysiol* 2015; **42:** 135–142.
6. Ogano M, Iwasaki YK, Tanabe J, Takagi H, Umemoto T, Hayashi M, et al. Antiarrhythmic effect of cardiac resynchronization therapy with triple-site biventricular stimulation. *Europace* 2013; **15:** 1491–1498.
7. Worley SJ, Gohn DC, Pulliam RW. Goose neck snare for LV lead placement in difficult venous anatomy. *Pacing Clin Electrophysiol* 2009; **32:** 1577–1581.
8. Soga Y, Ando K, Nobuyoshi M. Collateral approach for biventricular pacing of coronary sinus ostium obstruction. *Pacing Clin Electrophysiol* 2008; **31:** 122–124.
9. de Voogt WG, Ruiter JH. Occlusion of the coronary sinus: A complication of resynchronisation therapy for severe heart failure. *Europace* 2006; **8:** 456–458.
10. Ahmed K, Munawar M, Munawar DA, Hartono B, Damay V. Left ventricular lead positioning in cardiac resynchronization therapy: An innovative retrograde approach without using snare. *Europace* 2015; **17:** 495–498.
11. Abben RP, Chaisson G, Nair V. Traversing and dilating venous collaterals: A useful adjunct in left ventricular electrode placement. *J Invasive Cardiol* 2010; **22:** E93–E96.
12. Bali HK, Chattree KK, Bali SK, Chauhan HK, Shukla CP. Collateral approach for LV lead implantation in a case with abnormal venous anatomy. *Indian Heart J* 2013; **65:** 607–610.
13. Smith GT. The anatomy of the coronary circulation. *Am J Cardiol* 1962; **9:** 327–342.
14. von Ludinghausen M. The venous drainage of the human myocardium. *Adv Anat Embryol Cell Biol* 2003; **168:** I–VIII, 1–104.
15. Genain MA, Morlet A, Herrtage M, Muresian H, Anselme F, Latremouille C, et al. Comparative anatomy and angiography of the cardiac coronary venous system in four species: Human, ovine, porcine, and canine. *J Vet Cardiol* 2018; **20:** 33–44.
16. Hood WB Jr. Regional venous drainage of the human heart. *Br Heart J* 1968; **30:** 105–109.
17. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the

diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37:** 2129–2200.
18. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; **105:** 539–542.
19. Singh JP, Houser S, Heist EK, Ruskin JN. The coronary venous anatomy: A segmental approach to aid cardiac resynchronization therapy. *J Am Coll Cardiol* 2005; **46:** 68–74.
20. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, et al. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. *Circulation* 2011; **123:** 1159–1166.
21. Pakalska E, Kolff WJ. Anatomical basis for retrograde coronary vein perfusion. Venous anatomy and veno-venous anastomoses in the hearts of humans and some animals. *Minn Med* 1980; **63:** 795–801.
22. De Almeida MC, Spicer DE, Anderson RH. Why do we break one of the first rules of anatomy when describing the components of the heart? *Clin Anat* 2019; **32:** 585–596.
23. Mori S, Tretter JT, Spicer DE, Bolender DL, Anderson RH. What is the real cardiac anatomy? *Clin Anat* 2019; **32:** 288–309.
24. Habib A, Lachman N, Christensen KN, Asirvatham SJ. The anatomy of the coronary sinus venous system for the cardiac electrophysiologist. *Europace* 2009; **11**(Suppl 5)**:** v15–v21.
25. Fung JW, Yu CM, Yip G, Zhang Y, Chan H, Kum CC, et al. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. *Heart* 2004; **90:** 17–19.
26. Lambiase PD, Rinaldi A, Hauck J, Mobb M, Elliott D, Mohammad S, et al. Non-contact left ventricular endocardial mapping in cardiac resynchronisation therapy. *Heart* 2004; **90:** 44–51.
27. Gasparini M, Mantica M, Galimberti P, Bocciolone M, Genovese L, Mangiavacchi M, et al. Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy? *Pacing Clin Electrophysiol* 2003; **26:** 162–168.
28. Galand V, Singh JP, Leclercq C. Alternative left ventricular pacing approaches for an optimal cardiac resynchronization therapy. *Heart Rhythm* 2019; **16:** 1281–1289.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-20-0266