

Surgical Experience and Long-Term Results of Baroreflex Activation Therapy for Heart Failure With Reduced Ejection Fraction

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The purpose of this publication is to describe the intraoperative experience along with long-term safety and efficacy of the second-generation baroreflex activation therapy (BAT) system in patients with heart failure (HF) and reduced ejection fraction HF (HFrEF). In a randomized trial of New York Heart Association Class III HFrEF, 140 patients were assigned 1:1 to receive BAT plus medical therapy or medical therapy alone. Procedural information along with safety and efficacy data were collected and analyzed over 12 months. Within the cohort of 71 patients randomized to BAT, implant procedure time decreased with experience, from 106 ± 37 minutes on the first case to 83 ± 32 minutes on the third case. The rate of freedom from system- and procedure-related complications was 86% through 12 months, with the percentage of days alive without a complication related to system, procedure, or underlying cardiovascular condition identical to the control group. The complications that did occur were generally mild and short-lived. Overall, 12 months therapeutic benefit from BAT was consistent with previously reported efficacy through 6 months: there was a significant and sustained beneficial treatment effect on

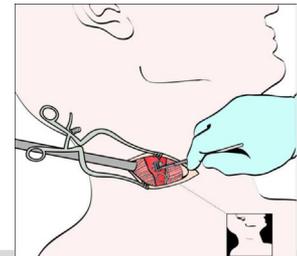


Illustration of second-generation BAT electrode implant.

Central Message

BAT system implantation is safe with the therapeutic benefits in heart failure being substantial and maintained for at least 1 year.

Perspective Statement

BAT system and implant techniques have evolved in a significantly positive direction from the first generation. With a pacemaker-like safety profile and therapeutic benefits in HFrEF sustained after 1 year, the necessary conditions are in place for an outcomes trial. A pivotal outcomes trial of BAT in HFrEF is expected to begin in 2016.

See Editorial Commentary pages XXX–XXX.

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New York Heart Association functional Class, quality of life, 6-minute hall walk distance, plasma N-terminal pro-brain natriuretic peptide, and systolic blood pressure. This was true for the full trial cohort and a predefined subset not receiving cardiac resynchronization therapy. There is a rapid learning curve for the specialized procedures entailed in a BAT system implant. BAT system implantation is safe with the therapeutic benefits of BAT in patients with HFREF being substantial and maintained for at least 1 year.

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INTRODUCTION

Patients with cardiovascular disease commonly present with issues associated with dysregulation of autonomic function. Pharmacologic therapies designed to address autonomic dysfunction have substantially improved outcomes and quality of life in patients with cardiovascular disease. Unfortunately, heart failure (HF) patient outcomes under the pharmacologic approach remain less than satisfactory, motivating development of implantable technologies designed to address persistent cardiovascular dysfunction. Implantable defibrillators and resynchronization devices have provided significant benefit in overall cardiac function for patients with reduced ejection fraction HF (HFREF). For end-stage cardiac dysfunction, left ventricular assist devices and ultimately cardiac transplantation are required. However, a significant treatment chasm exists between cardiac rhythm management devices and mechanical circulatory support or transplant in invasiveness and severity of patient illness. Thus, additional therapeutic options are needed for patients with HFREF who require options beyond defibrillation and resynchronization, but are not yet sufficiently compromised to require ventricular assist and transplantation.

Several implantable devices are presently under investigation to fill this treatment gap in HFREF including baroreflex activation therapy (BAT), which has shown to significantly improve ejection fraction, plasma biomarkers, health care resource use, functional capacity, New York Heart Association (NYHA) functional class, and quality of life. Recent publications indicate that BAT improves the clinical course of patients with HFREF, including a Phase II randomized controlled trial^{1,2} and a Phase I trial that has reported sustained benefit through at least 21 months.^{3,4} The baroreflex pathway has been used historically to significant benefit by both medical^{5,6}

and device⁷ therapies, but limitations have prevented widespread use. This report describes in detail the surgical and anesthetic management of patients randomized to receive BAT device implantation. Additionally, 1-year rates of device-related complications, overall complications and effectiveness of BAT would be compared with patients randomized to guideline-directed medical therapy (GDMT).

METHODS

BAT System and Implant Procedure

BAT is delivered by a second-generation system (Barostim neo, CVRx, Inc, Minneapolis, MN), which has been previously described in detail.⁸ Briefly, it consists of a pulse generator similar in size and shape to an implanted defibrillator coupled with a carotid sinus lead. The miniaturized distal end of the lead includes a 7 mm circular electrode backer with a 2 mm-diameter disk electrode at the center. The reverse side of the backer has an eyelet-like silicone “buckle” that is used for electrode positioning with a customized mapping tool. Activation and configuration of the system are accomplished wirelessly using a dedicated programmer, comprised by a laptop computer, custom software, and a transceiver unit connected by universal serial bus.

Preparation for surgery begins well in advance of implant. Cardiovascular medications are stopped 4-6 hours before surgery with the exception of beta-blocker therapy, which is down-titrated 1-2 days in advance to a level at which intraoperative bradycardia is not expected to interfere with observation of the baroreflex response. Dual antiplatelet therapy is reduced to monotherapy and anticoagulants are discontinued to reduce risk of bleeding complications. Owing to the withholding of cardiovascular medications, BAT system implant should be scheduled as the first case of the day so that medical

therapy can be restarted postprocedure. A prophylactic antibiotic is given, usually a cephalosporin, administered within 1 hour of the skin incision.

Implantation of the BAT system requires close collaboration across disciplines, particularly among the surgical and anesthesia teams. The implantation procedure can be conceptualized as occurring in 2 phases, a first phase in which mapping of the carotid sinus is performed to determine the lead placement, which provides maximum nerve stimulation and a second phase during which the actual implantation of the device occurs. So as not to blunt the baroreflex pathway during the mapping phase, an anesthesia regimen, which does not use inhalation anesthesia with the exception of nitrous oxide, is employed. The patient is premedicated with 0.5-1.0 mg of midazolam. Induction is achieved with 0.1-0.2 mg/kg midazolam, 0.2-0.3 mg/kg etomidate, and 0.025 µg/kg/min of fentanyl over 10 minutes. Intubation is facilitated with 0.3-0.6 mg/kg of rocuronium. The patient is maintained during the remainder of the first phase with 0.1-0.4 mg/kg/h of midazolam and 0.05-0.30 µg/kg/min fentanyl or morphine as required.

The first phase begins by exposing the carotid artery bifurcation. The right carotid is preferentially used for placement of the carotid sinus lead as earlier studies have documented an increased sensitivity to BAT on the right when compared with the left carotid.⁹ Patient positioning is similar to that used for a carotid endarterectomy with the patient's chin rotated approximately 45° away from the operating surgeon. Before the incision, ultrasonography is used to locate the carotid bifurcation. A 2-3 cm transverse, skin crease incision is made directly over the bifurcation. Exposure of the bifurcation is achieved by mobilizing the sternocleidomastoid muscle and internal jugular vein. Division of the facial vein is usually required to provide sufficient exposure. Anterior exposure of the bifurcation and the proximal internal carotid is all that is required in most patients. Circumferential dissection of the bifurcation, which was mandatory for implantation of the first-generation BAT device,^{10,11} is not required.

With exposure completed, mapping of the carotid sinus is initiated. Targeted for stimulation are the sensory endings of the carotid sinus nerve, which arborize the carotid sinus, the baroreceptors. A recent anatomical study¹² demonstrated that the highest concentration of baroreceptors is typically located along the medial portion of the proximal internal carotid artery (Fig. 1, site A). Thus, mapping generally begins on the anteromedial surface of the internal carotid artery with the electrode held in place by a wand-like implant tool. The electrode is

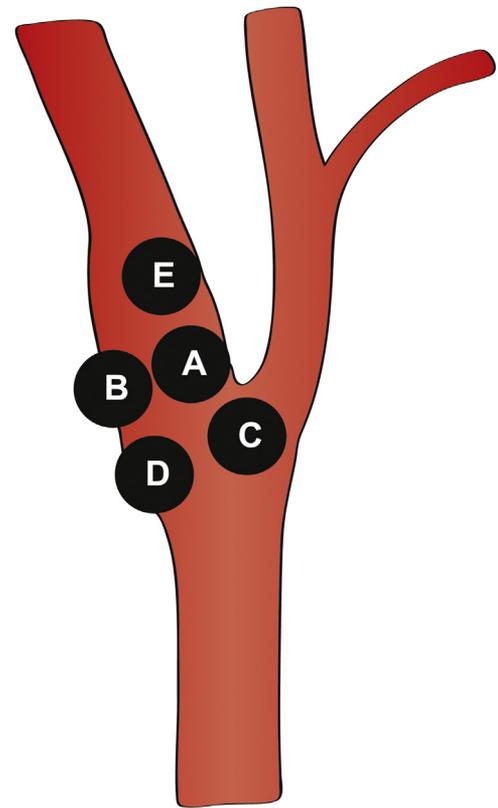


Figure 1. Standardized mapping locations for carotid sinus electrode, in recommended sequence A-E on the internal carotid artery and carotid bifurcation. If no anterior location is determined to be suitable mapping may be continued on the posterior surface. (Color version of figure is available online at <http://www.semthorcardiovascsurg.com>.)

connected via lead wire to the pulse generator, which is programmed with initial settings of 6 mA pulse amplitude and 125 µs pulse width at a rate of 80 pulses per second. Stimulation is activated to test the baroreflex response, evidenced by decreasing heart rate and systolic blood pressure (SBP). Additional locations may be sequentially interrogated along the internal carotid artery and carotid bifurcation as shown in Figure 1 to determine the maximum baroreflex response. In a rare patient, posterior dissection of the carotid bifurcation may be required to optimize carotid sinus nerve stimulation. Stimulation pulse amplitude may be increased if necessary to clarify the optimal location.

For successful mapping, communication between the surgeon and anesthesiologist is critical because mapping of possible electrode locations is determined by observing hemodynamic responses to carotid sinus nerve activation. Before the initiation of mapping, stable heart rate, and blood pressure should be established as a baseline. The degree of baroreflex response is determined by observed

decreases in heart rate and blood pressure. In patients with HFREF, these changes from baseline may be subtle. Heart rate responses are frequently rapid and distinct if the patient has intact conduction and is not pacemaker dependent. Blood pressure responses from reduced sympathetic tone are also observable, although HFREF patients are typically normotensive at baseline. Peak responses in heart rate and pressure generally occur within 30-120 seconds of initiating stimulation.

With the carotid sinus location of maximum baroreflex response established, the electrode is anchored by a series of 5-6 6-0 monofilament sutures penetrating the edge of the electrode backer and the adventitia of the carotid artery. Once secured, the proper placement of the electrode is verified by observing an appropriate hemodynamic response to stimulation with satisfactory impedance. Low impedance or failure to observe hemodynamic changes may require repositioning of the electrode and possibly additional mapping. Following satisfactory electrode positioning, anesthesia management may include inhalation anesthetics if necessary. Additional sutures are then placed to tether the lead to the common carotid artery. The buckle used to attach the implant tool is removed. **Figure 2** provides an illustration of the fixed electrode with the mapping tool and buckle present.

With the electrode in place, an infraclavicular subcutaneous chest wall pocket ipsilateral to the lead is created for the pulse generator. The pocket is sized

to accommodate both the pulse generator and any excess lead length. The lead is then routed either anterior to the sternocleidomastoid, or through the space between the sternal and clavicular heads of the sternocleidomastoid muscle and subcutaneously anterior to the clavicle to the pocket. The lead terminus is connected to the pulse generator. The pulse generator is placed in the pocket and excess lead is coiled and placed medial to the pulse generator. The pulse generator is secured in the pocket with 2 sutures placed through suture holes in the device header and fascia of the pectoralis major.

After completing implantation, a nose-to-nipples radiograph is recommended to document the position of the implanted system. An additional dose of antibiotics is given and cardiovascular medications are resumed.

Patients, Study Design, and Statistical Analysis

The design and eligibility criteria for the BAT in HFREF trial have been previously reported.¹ Briefly, patients with NYHA Class III HF and left ventricular ejection fraction $\leq 35\%$ receiving GDMT were eligible if resting heart rate was controlled, estimated glomerular filtration rate was ≥ 30 mL/min/1.73 m² and 6-minute hall walk distance (6 MHW) was 150-450 m. Patients were excluded if they were not suitable surgical candidates, had a carotid bifurcation at the mandible, exhibited significant ($> 50\%$) common, or internal carotid stenosis, had recently decompensated HF or received other HF device therapies. The protocol conformed to the Declaration of Helsinki and was approved by ethics committees, institutional review boards, and regional authorities in and outside the United States.

Patients were randomized 1:1 to receive BAT + GDMT or GDMT alone. Efficacy between the 2 arms was measured by changes in surrogate or intermediate variables including 6 MHW, NYHA Class, serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level, and quality of life from the Minnesota Living with Heart Failure Questionnaire (QOL) at 12 months. Comparison of the 2 arms in efficacy was explored in 2 ways. First, pairwise differences were calculated between 12 months and baseline values within each group to assess consistency with previously reported results at 6 months. Secondly, a repeated-measures model measuring change from baseline was constructed using 6- and 12-month results. From this model, the sustained treatment effect of BAT + GDMT vs GDMT alone was computed and tested for significance. A $P < 0.05$ was accepted as indicating statistical significance.

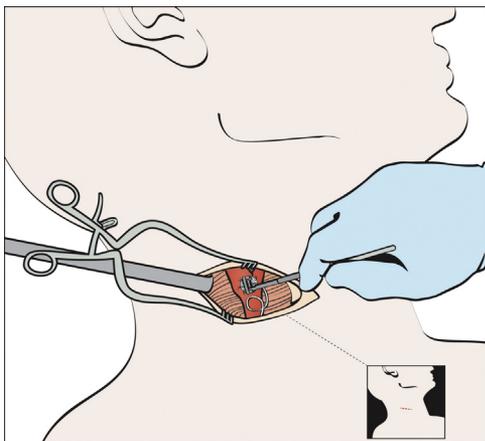


Figure 2. Illustration of carotid sinus electrode implant. An incision centered on the carotid bifurcation is made just large enough to expose the anterior surface. The mapping tool is manually guided to establish the optimal electrode location. Once determined, the electrode is fixed with sutures placed around the perimeter of the electrode backer. (Color version of figure is available online at <http://www.semthorcardiovascsurg.com>.)

Safety of the BAT procedure was assessed through a composite measure of any major adverse neurologic and cardiovascular events (MANCE) within 30 days and 12 months of the procedure.¹ Other device- and procedure-related complications were recorded as well at 30 days and 12 months. Adverse event rates in the GDMT group were recorded and compared. To further assess overall HF and HF treatment-related safety, the percentage of days alive through 12 months without an unresolved complication related to the device, the implant procedure, or the patient's underlying cardiovascular condition was computed for the BAT + GDMT and GDMT groups.

RESULTS

As previously reported,¹ a total of 146 patients were randomized into the trial from 45 centers over 23 months (Fig. 3). Of these, 76 were randomized to BAT + GDMT and 70 to GDMT alone. Implant occurred in 71 of the 76 BAT + GDMT patients whereas 1 GDMT patient died before the activation date. Thus, the trial cohort consisted of 140 patients. Baseline characteristics were generally well balanced between the groups.

Mean procedure time was 99 ± 35 minutes, of which mapping comprised 36 ± 24 minutes. Both total procedure time and intraprocedural mapping time decreased with experience, with a mean implant and mapping time at the first procedure performed by a center of 106 ± 37 and 41 ± 23 minutes, respectively, decreasing to 83 ± 32 and 20 ± 14 minutes by the third procedure. Regression analysis of all cases revealed a significant trend toward duration reduction with case number for both overall procedure and mapping times (both $P < 0.001$).

In the United States trial cohort, electrode implant location was collected according to a 4-position schematic ($N = 37$, Fig. 4). Most (70%) electrodes

were implanted anteromedially on the internal carotid artery just cranial of the bifurcation. Average electrode impedance was $804 \pm 272 \Omega$ upon completion of fixation. Maximum intraoperative hemodynamic responses averaged -12 ± 8 mm Hg for SBP from a baseline of 117 ± 21 mm Hg ($N = 51$) and -8 ± 10 bpm for heart rate from an average of 61 ± 13 bpm ($N = 50$).

A total of 101 patients completed 12 months of follow-up (57 BAT + GDMT, 44 GDMT, Fig. 3). The rate of all-cause mortality was slightly higher in the GDMT group, with 8 patients dying as compared with 7 in the BAT + GDMT group. Missed visits were also similar, with 3 in the GDMT group vs 2 in the BAT + GDMT group. The largest difference in attrition was because of a higher withdrawal rate in the GDMT arm, in which 14 patients discontinued participation, vs the BAT + GDMT arm, from which 5 patients withdrew.

Significant beneficial treatment effects in SBP, NT-proBNP, 6 MHW, QOL, and NYHA Class observed at 6 months were sustained through 12 months, both for the study population as a whole as well as the prespecified no Cardiac-Resynchronization Therapy (CRT) cohort (Table 1). In the no-CRT cohort, improvement in NYHA Class for BAT + GDMT reached statistical significance, a finding not observed in the 6-month analysis. Applied dose of BAT was likewise stable during the period from 6-12 months, with average applied power at $290 \pm 210 \mu\text{W}$ and $280 \pm 210 \mu\text{W}$, respectively. Average pulse generator lifetime, including actual device replacements and a conservative estimate for time of elective replacement, was 39.3 months.

System- and procedure-related MANCE have been previously reported through 6 months.¹ Briefly, there were 2 MANCE events for an overall event-free rate of 97.2% over 6 months. Both MANCE events were hematomas, which resolved with no residual side

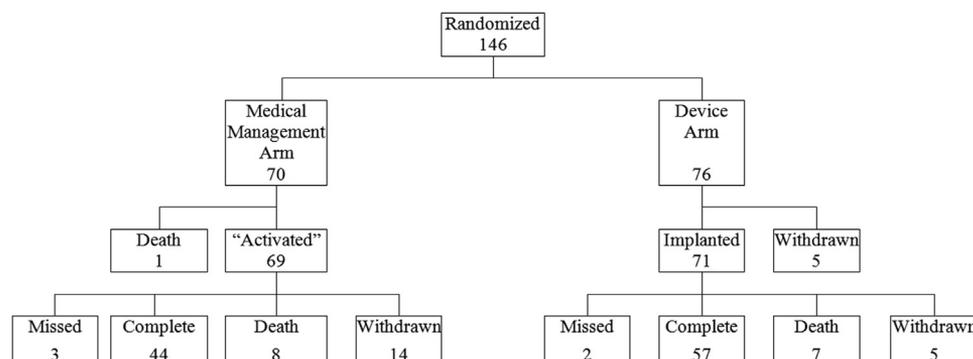


Figure 3. Trial flow diagram through 12 months of follow-up. Data were available for 57 patients randomized to BAT device plus guideline-directed medical therapy and 44 patients randomized to guideline-directed medical therapy alone.

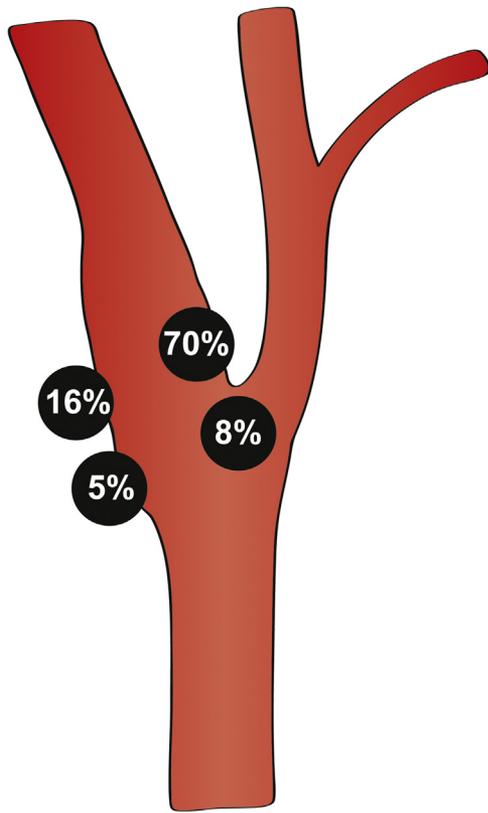


Figure 4. Optimized placement of carotid sinus electrode among US trial participants ($N = 37$). Most electrodes are implanted in an anteromedial location adjacent to the carotid bifurcation. (Color version of figure is available online at <http://www.semthorcardiovascsurg.com>.)

effects. No system- or procedure-related MANCE events occurred from 6-12 months. The rate of freedom from system- and procedure-related complications was 85.9%, with all but 1 event, transection of a transverse cervical skin nerve, documented as occurring within 7 days of surgery (Table 2). Many complications were typical of patients with HF undergoing device implantation, such as hypotension and urinary issues. Likewise as in pacemaker implant, a hematoma occasionally formed in the pulse generator pocket (2 cases). Totally, 2 of the procedure-related complications illustrated the importance of proper training and coordination. In 1 case, a pneumothorax was created when a hypodermic needle used as a temporary return electrode in the mapping process was advanced into an intercostal space. In the second case, the skin nerve transection led to a persistent numb feeling in the area of the neck incision. This was the only complication associated with implant of the carotid sinus lead.

With respect to overall HF and HF treatment-related safety, the percentage of days alive without a complication related to the patient's underlying cardiovascular condition, the device or the procedure was not significantly different. The mean percentage of days free from these complications was 92.1% for both the BAT + GDMT and GDMT groups ($P = 1.00$).

DISCUSSION

Surgical complexity, duration, and safety of BAT system implantation have improved significantly

Table 1. 12-Month Change From Baseline in Clinical Variables (A) for all Randomized HF Patients and (B) for HF Patients Without Concomitant CRT. The Differences in Sample Size are Because of Missed Visits, Incomplete Testing, or Missing Measurements at the 12-Month Visit. Data are Presented as Mean \pm SE or Median (IQR). Repeated-Measures Model Assesses Consistency of Results by Including Measurements at 6 Months

Parameter	BAT + GDMT (N/Value)		GDMT (N/Value)		Repeated-Measures Model	P Value
<i>(A) All Randomized HF Patients</i>						
SBP (mm Hg)	57	+2.1 \pm 2.4	44	-4.3 \pm 2.4	+5.6 \pm 2.4	0.02
NT-proBNP (pg/mL)	37	-18.6 (-824, 288)	34	+259.5 (-244, 905)	-163*	0.008
6 MHW (m)	50	+58.5 \pm 17.0	39	+13.4 \pm 17.9	+53 \pm 19	0.005
QOL (points)	56	-9.9 \pm 2.9	42	+0.7 \pm 2.9	-10.7 \pm 3.5	0.003
NYHA (%Improved)	56	+45	42	+26	OR = 3.73	<0.001
<i>(B) HF Patients Without Concomitant CRT</i>						
SBP (mm Hg)	38	+4.2 \pm 3.1	31	-4.0 \pm 2.5	+6.5 \pm 2.9	0.03
NT-proBNP (pg/mL)	24	-102 (-1141, 134)	25	+152 (-314, 866)	-160*	0.01
6 MHW (m)	33	+86.6 \pm 20.8	28	+20.7 \pm 24.4	+77 \pm 24.7	0.003
QOL (points)	37	-13.6 \pm 3.6	31	+1.2 \pm 3.3	-17 \pm 4.6	<0.001
NYHA (%Improved)	37	+49	31	+29	OR = 2.98	0.005

OR, odds ratio.

*The repeated-measures computation for NT-proBNP does not provide a CI or standard error.

Table 2. System- and Procedure-Related Complications and Major Adverse Neurological and Cardiovascular Events (MANCE) Though 12 Months

Days From Implant	Event	Procedure Related	System Related
0	Urinary retention	X	
0	Bradycardia with hypotension	X	X
0	Paroxysmal atrial tachycardia		X
0	Atrial fibrillation with hypotension*	X	
0	Worsening of existing HF and pulmonary hypertension	X	
0	Pneumothorax	X	
1	Urinary tract infection secondary to urinary retention	X	
1	Postoperative infected hematoma*†	X	X
1	Hypotension	X	
7	Pulse generator pocket hematoma†	X	X
127	Transection of the transverse cervical skin nerve	X	

*Events occurred in the same patient.

†MANCE events.

from the first-generation system. Overall, implant time including mapping time for the first-generation system averaged approximately 200 and 120 minutes, respectively, in early reports from patients with resistant hypertension.^{10,11} The present results demonstrate that total procedure time has declined by half and mapping time has decreased by more than a factor of 3. These improvements are due to several factors. First, the second-generation system requires only a unilateral implant as opposed to an obligatory bilateral electrode implant. Secondly, implant of the second-generation electrode generally requires only an anterior exposure of the carotid sinus, whereas the first-generation system required full circumferential dissection of the carotid bifurcation and proximal internal carotid artery. Third, experience has led to recognition that dissection of the periadventitia—common in implants of the first-generation system—is not necessary for a reliable interface between the electrode and the carotid sinus nerve endings containing baroreceptors. Finally, additional knowledge regarding location of baroreceptors has led to right carotid bifurcation exposure with anteromedial placement of the electrode being the preferred approach.

Reduced procedure complexity and duration have, in turn, improved the system safety profile. In the Rheos Pivotal Trial of the first-generation BAT system in resistant hypertension, the rate of freedom from procedure-related complications was 74.8%, and the rate of freedom from device-related complications through 12 months was 87.2%.¹³ Noteworthy among the complications were 4.8% of patients receiving cranial nerve injuries with residual deficits.¹³ In the present trial, the system- and procedure-related complication-free rate was 85.9%, with no cranial nerve injuries. Importantly,

this improved safety result was observed in patients with HF, who have inherently higher surgical risk than the patients with hypertension studied in the Rheos Pivotal Trial. Overall, the second-generation system safety profile is comparable with that of a cardiac pacemaker implant.¹⁴ The safety profile may be further enhanced by increased battery life, decreasing the requirement for changes of the pulse generator. The average stimulator lifetime for the second-generation system exceeds 3.25 years, whereas typical longevity for the first-generation system was approximately 1.5 years. For overall HF and HF treatment-related complications, BAT + GDMT and GDMT patients did not differ. This is an important finding given that BAT + GDMT patients were subjected to surgery with the potential for procedure-associated complications.

As previously reported, the trial met its primary efficacy end point at 6 months of follow-up. Compared with patients receiving GDMT alone, GDMT + BAT patients showed improvements in NYHA class ranking ($P = 0.002$ for change in distribution), QOL score (-17.4 ± 2.8 points vs 2.1 ± 3.1 points; $P < 0.001$), and 6 MHW (59.6 ± 14.1 m vs 1.5 ± 13.2 m; $P = 0.004$).¹ NT-proBNP and blood pressures also demonstrated improvement. Measurements of clinical status at 12 months indicate that BAT effectiveness is sustained. Sustained beneficial treatment effects in NT-proBNP, 6 MHW, QOL, NYHA Class, and SBP were both statistically and clinically significant. These findings were true for the Phase II cohort as a whole as well as for the prespecified no-CRT subgroup. Thus, the Phase II study results of 12-month duration validate the recent report from the Phase I study of long-term benefits, which were sustained in that cohort for at least 21 months.⁴

Limitations and Future Work

Although the Phase I and II trials both confirm the long-term benefits of BAT in HFrEF, the present knowledge base needs to be expanded. The Phase I trial was open-label and consisted of 11 patients whereas the Phase II trial consisted of 140 patients and used a medical management control group. Thus, the magnitude of benefit relative to sham is undetermined. Reductions in muscle sympathetic nerve activity (Phase I) and NT-proBNP (Phase II) provide objective evidence that corroborates therapy benefit even in the absence of control. Although these results bode well for an outcomes trial, actual results should be accrued on a significant number of patients to confirm reductions in cardiovascular mortality and HF hospitalization. This is the aim of a pivotal trial planned to begin enrollment in 2016.

Although the BAT system and implant techniques have evolved in a significantly positive direction from the first generation, opportunities for further improvement exist. Because the most common electrode locations are known and 1 region in particular has become a de facto starting position for mapping, it is conceivable that an electrode could be developed to cover the locations where a response is most likely. If anatomical landmarks coupled with a versatile electrode design were to obviate the need for mapping, not only would procedure time diminish, but also the complexity of anesthesia would be substantially reduced. Additionally, despite the fact that the suturing technique required to fix the BAT electrode is well within the capabilities of a vascular or cardiac surgeon, the process can be time-consuming. If the number of required sutures could be reduced through a design change or the use of

adjunctive fixatives or both, the procedure would also be simplified and shortened.

BAT is presently available for commercial use in resistant hypertension and HFrEF in regions that accept evidence commensurate with CE-Marking. Investigational plans are also in place to extend BAT availability for those conditions in the United States. Meanwhile, evidence suggests that BAT may be a useful treatment in chronic kidney disease^{15,16} and HF with preserved Ejection Fraction.¹⁷⁻¹⁹

CONCLUSION

The procedure required to implant the second-generation BAT system is unique and requires teamwork across specialties and attention to detail. Evidence from the recent Phase II trial of BAT in HFrEF indicates that with the proper training, the procedure is safe with a short-learning curve. Long-term experience from the Phase II trial indicates that the BAT system is safe to use, with a pacemaker-like safety profile. For BAT efficacy, 12 months result from the randomized, controlled Phase II trial indicate significant clinical improvement in the patients receiving BAT, confirming previous reports from the Phase I and Phase II cohorts. The level of evidence supporting BAT in HFrEF and the maturity of the second-generation system indicates that the necessary conditions are in place for an outcomes trial. A pivotal outcomes trial of BAT in HFrEF is expected to begin in 2016.

SUPPLEMENTARY MATERIALS

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1053/j.semctvs.2016.04.017>.

1. Abraham WT, Zile MR, Weaver FA, et al: Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 3:487-496, 2015
2. Zile MR, Abraham WT, Weaver FA, et al: Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: Safety and efficacy in patients with and without cardiac resynchronization therapy. *Eur J Heart Fail* 17:1066-1074, 2015
3. Gronda E, Seravalle G, Brambilla G, et al: Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: A proof-of-concept study. *Eur J Heart Fail* 16: 977-983, 2014
4. Gronda E, Seravalle G, Trevano FQ, et al: Long-term chronic baroreflex activation: Persistent efficacy in patients with heart failure and reduced ejection fraction. *J Hypertens* 33: 1704-1708, 2015
5. Ferguson DW, Berg WJ, Sanders JS, et al: Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. *Circulation* 80:65-77, 1989
6. Rathore SS, Curtis JP, Wang Y, et al: Association of serum digoxin concentration and outcomes in patients with heart failure. *J Am Med Assoc* 289:871-878, 2003
7. Braunwald E, Epstein SE, Glick G, et al: Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves. *N Engl J Med* 277: 1278-1283, 1967
8. Hoppe UC, Brandt MC, Wachter R, et al: Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: Results from the Barostim neo trial. *J Am Soc Hypertens* 6:270-276, 2012
9. de Leeuw PW, Alnima T, Lovett E, et al: Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension* 65:187-192, 2015
10. Tordoir JH, Scheffers I, Schmidli J, et al: An implantable carotid sinus baroreflex activating system: Surgical technique and short-term outcome from a multi-center feasibility trial for the

- treatment of resistant hypertension. *Eur J Vasc Endovasc Surg* 33:414-421, 2007
11. Illig KA, Levy M, Sanchez L, et al: An implantable carotid sinus stimulator for drug-resistant hypertension: Surgical technique and short-term outcome from the multicenter phase II Rheos feasibility trial. *J Vasc Surg* 44: 1213-1218, 2006
 12. Toorop RJ, Ousrout R, Scheltinga MR, et al: Carotid baroreceptors are mainly localized in the medial portions of the proximal internal carotid artery. *Ann Anat* 195: 248-252, 2013
 13. Bisognano JD, Bakris G, Nadim MK, et al: Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 58:765-773, 2011
 14. Udo EO, Zuithoff NP, van Hemel NM, et al: Incidence and predictors of short- and long-term complications in pacemaker therapy: The FOLLOWPACE study. *Heart Rhythm* 9: 728-735, 2012
 15. Wallbach M, Lehnig LY, Schroer C, et al: Impact of baroreflex activation therapy on renal function—A pilot study. *Am J Nephrol* 40: 371-380, 2014
 16. Beige J, Koziolok MJ, Hennig G, et al: Baroreflex activation therapy in patients with end-stage renal failure: Proof of concept. *J Hypertens* 33:2344-2349, 2015
 17. Georgakopoulos D, Little WC, Abraham WT, et al: Chronic baroreflex activation: A potential therapeutic approach to heart failure with preserved ejection fraction. *J Card Fail* 17: 167-178, 2011
 18. Brandt MC, Madershahian N, Velden R, et al: Baroreflex activation as a novel therapeutic strategy for diastolic heart failure. *Clin Res Cardiol* 100:249-251, 2011
 19. de Leeuw P, Bakris G, Haller H, et al: Baroreflex activation therapy improves status of resistant hypertension patients with heart failure. *Eur Heart J* 35:843, 2014