11 Electrogram–Guided Ablation

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In 1994, Swartz et al. (1) ushered in an era of incredible growth in the understanding and treatment of atrial fibrillation (AF) with their introduction of a catheter-based MAZE procedure. Astute observations, such as those made by Haïssaguerre et al. (2), in the recognition of the importance of the pulmonary veins (PVs), have helped develop and refine the catheter-based MAZE to instead target triggers arising from the PVs. Several other laboratories around the world have worked extensively to create the best approach for the ablation of AF while focusing on the important role played by the PVs (3–6). However, the weakness in this strategy is the assumption that all patients with AF have the same underlying mechanism. Certainly PV-related triggers play a significant role in patients who have paroxysmal AF, but this does not address the increasing numbers of patients who have persistent or permanent AF and who are now seeking ablative therapies. It behooves us to seek and understand the multiple components of AF triggering, initiating, and perpetuation that will allow us to tailor our procedure to the individual.

Mechanisms of Atrial Fibrillation

Ideally, one would eradicate triggers and eliminate or modify the substrate that initiates and perpetuates AF. Focusing on the elimination of triggers that are electrically active at the time of ablation is not sufficient given the possible interplay of other mechanisms—and these strategies have had only moderate success (7–9).

Triggers of AF include PACs, which may arise from any area of the left or right [Au1] atria, the superior vena cava (SVC), inferior vena cava (IVC), the coronary sinus (CS), or any of the four PVs (2,10–12). These abnormal impulses "trigger" an initiating rhythm, which may include an atrial tachycardia (AT), atrioventricular nodal re-entry tachycardia (AVNRT), atrioventricular re-entry tachycardia (AVRT), or atrial flutter (AFl). Any of these arrhythmias or the triggers themselves may lead to an unstable AF, which depends on electrically abnormal substrate (predominately involving the left atrium [LA] and CS to perpetuate as stable AF) (Fig. 11.1). Strategies to abolish or modify the final common pathway in the development of AF should be the most
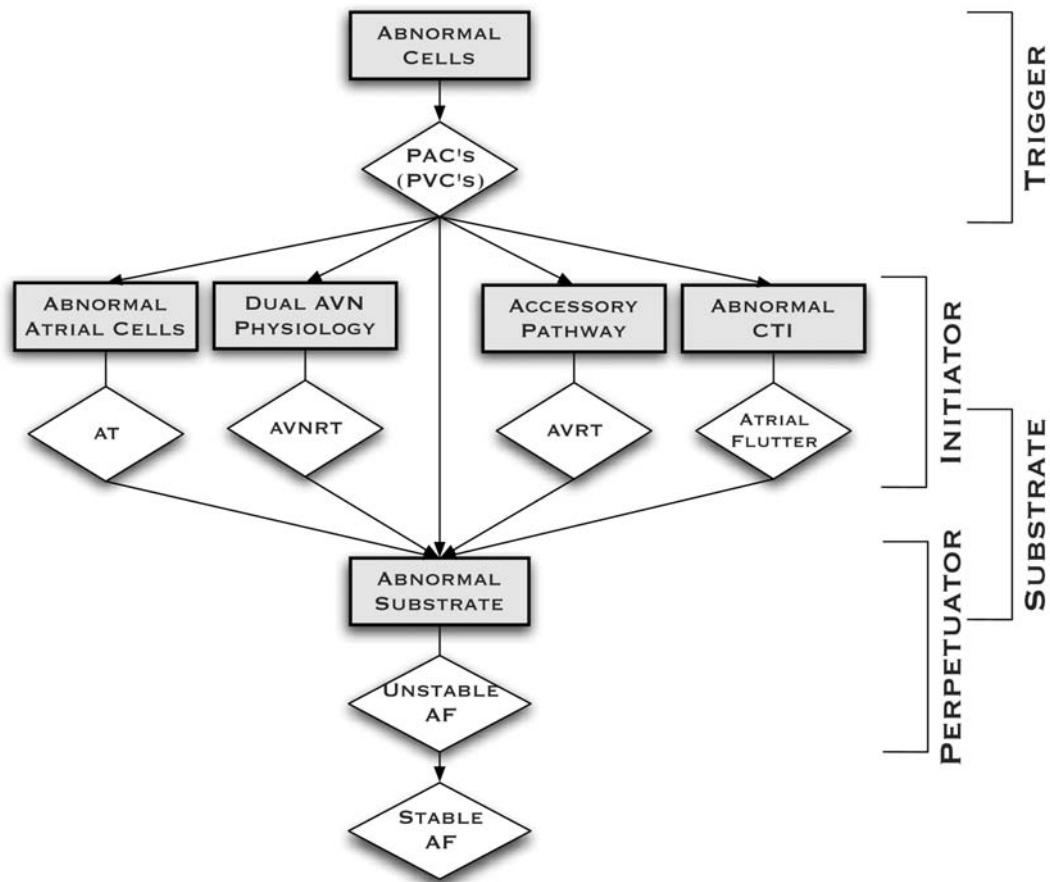
Figure 11.1. The development of AF depends on the complex interaction of triggering impulses (often from the PVs), which initiate abnormal arrhythmias including AT, AVNRT, AVRT, AFl, or unstable AF. The final step in the perpetuation of stable AF requires interplay between an initiating arrhythmia and abnormal substrate.

successful, but challenges still exist. Current methods of substrate modification rely on debulking atrial tissue with catheter-based lines of scar formed by widely encircling endocardial lesions created around PVs by radiofrequency (RF) ablation (3–6), or by an open-chest ablation (endocardial or epicardial) or cut-and-sew method (13). Most techniques for the less-invasive catheter-based procedures still rely primarily on the idea of PV isolation and substrate modification only results secondarily. The era of "burn and learn" is coming to an end and now we must target our ablations to address the mechanisms behind AF. To this end, areas of complex fractionated atrial electrograms have been identified as important substrate targets whose elimination can result in successful treatment of AF (14).

Definition of Complex Fractionated Atrial Electrograms

Complex fractionated atrial electrograms (CFAE) are low-voltage signals (0.04–0.25 mV) defined as either: (a) atrial electrograms that are fractionated and

Figure 11.2. CFAEs are composed of two deflections or more and/or have a perturbation of the baseline with continuous deflections from a prolonged activation complex; or are associated with a very short cycle length (≤120 ms). The ablation catheter (*ABL d*) is used to map and ablate the CFAE. The most highly fractionated electrograms can be seen in this example to exist on the LA septal wall although they still exist in the CS os and LIPV antrum. The local electrograms at the RSPV antrum are less fractionated, but have a very short cycle length and this may represent a "driver." CS, coronary sinus; LA, left atrium; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein.

composed of two deflections or more and/or have a perturbation of the baseline with continuous deflections from a prolonged activation complex; or (b) atrial electrograms with a very short cycle length (≤120 ms) with or without multiple potentials when compared with the atrial cycle length recorded from other parts of the atria (14) (Fig. 11.2).

Mechanisms of Complex Fractionated Atrial Electrograms

The underlying etiology of CFAE has not yet been elucidated, but several theories are being investigated. Pioneering work by Wells et al. (15) identified four types of atrial electrograms that may be present in AF:

- Type I: Discrete complexes separated by an isoelectric baseline free of perturbation.
- Type II: Discrete complexes but with perturbations of the baseline between complexes.
- Type III: Fractionated electrograms that fail to demonstrate either discrete complexes or isoelectric intervals.
- Type IV: Electrograms of Type III alternating with periods characteristic of Type I and/or Type II electrograms.

Konings et al. (16) applied this knowledge during intraoperative studies and identified three types of AF based on their mechanism of propagation:

- Type I: Single broad-wave fronts propagating without significant conduction delay, exhibiting only short arcs of conduction block or small areas of slow conduction not disturbing the main course of propagation.
- Type II: Activation patterns characterized either by single waves associated with a considerable amount of conduction block and/or slow conduction or the presence of two wavelets.
- Type III: Presence of three or more wavelets associated with areas of slow conduction (<10 cm/s) and multiple arcs of conduction block.

Despite the elaborate descriptions of CFAE, a true explanation for their existence did not exist until very recently.

The work in sheep by Kalifa et al. (17), has shown a key relationship between areas of dominant frequency and areas of fractionation. They were able to localize areas with regular, fast, spatiotemporally organized activity and map the regions around them. Waves propagating from these areas were found to break and change direction recurrently at a boundary zone and demonstrate fractionation of local electrograms. One of the key electrophysiologic mechanisms for AF that was confirmed by their work relates to the hypothesis that high-frequency re-entry at the boundary zones is responsible for the fractionation.

The most prominent theory underlying the occurrence of CFAE involves the complex interplay of the intrinsic cardiac nervous system on atrial tissues. The cardiac ganglionic plexi (GP) are a collection of autonomic nervous tissues with afferent and efferent sympathetic and parasympathetic fibers (18,19). There are six major GPs that may exert influence on the atria (Fig. 11.3):

1. superior LA
2. posterolateral LA
3. posteromedial LA
4. anterior descending
5. posterior RA
6. superior RA

In animal models, the stimulation of parasympathetic fibers within the GP has been shown to decrease atrial effective refractory periods (ERP) and allow AF to perpetuate (20). Simultaneously, stimulation of sympathetic fibers may occur in similar areas, which can initiate PV ectopy (21). Unfortunately, mapping and ablating the GP is time consuming and difficult. Ongoing research has identified a close relationship between the location of CFAE and the GP in animal models (20–22). CFAE-targeted ablation may provide a surrogate for modification of the GP if this relationship can be confirmed in humans. Certainly, ablation in areas that have resulted in a vagal response has been shown to provide excellent results in the treatment of AF (23).

Location of Complex Fractionated Atrial Electrograms

Within an individual, there exists temporal and spatial stability of CFAE, which facilitates accurate mapping. These regions are not symmetrically located within the atria
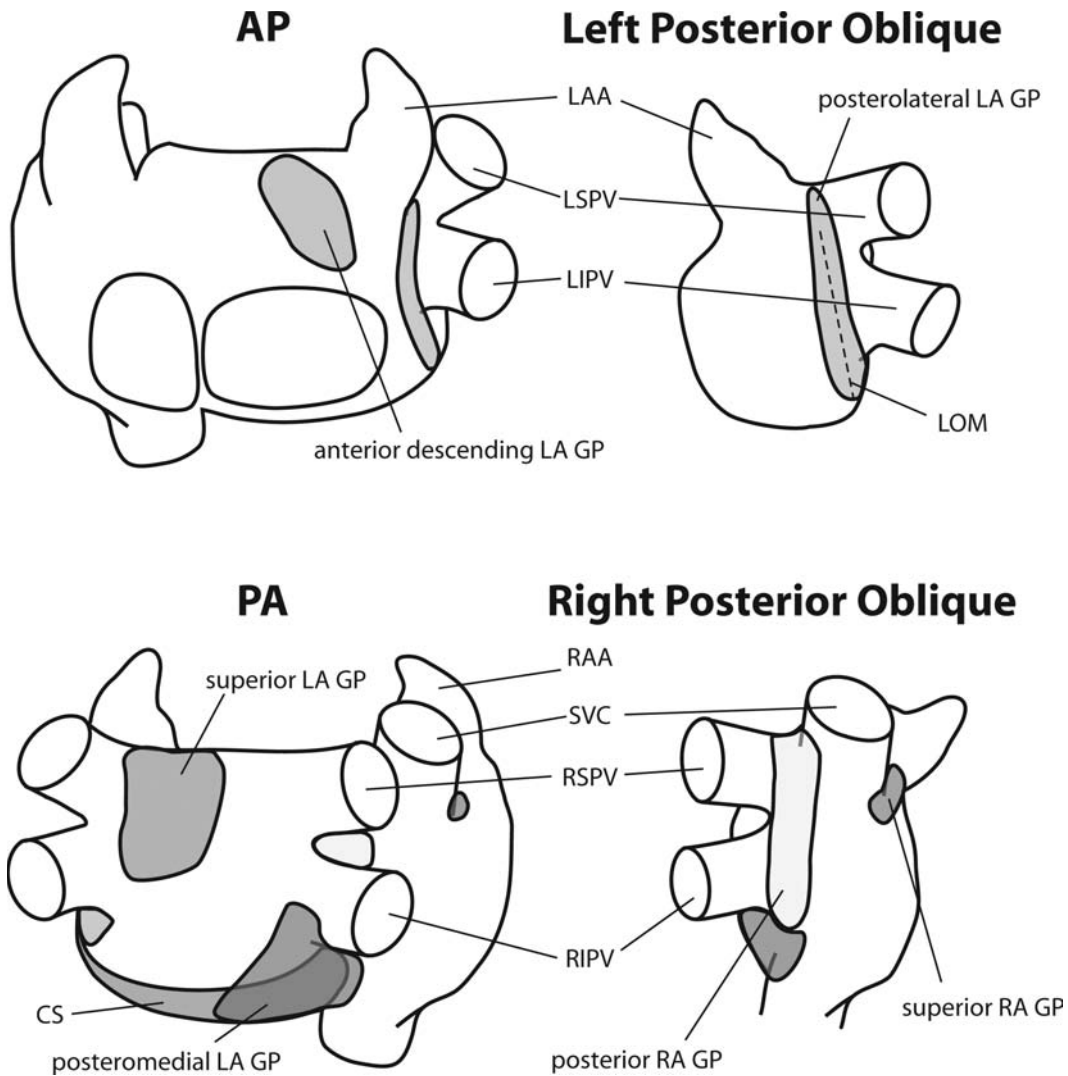
Figure 11.3. Six cardiac ganglionic plexi (GP) are located on or near the left and right atria and have been shown to exhibit influence on the initiation and perpetuation of AF: superior left atrial GP, posterolateral left atrial GP; posteromedial left atrial GP, left anterior descending GP, posterior right atrial GP, and superior right atrial GP. LAA, left atrial appendage; RAA, right atrial appendage; CS, coronary sinus; LOM, Ligament of Marshall; SVC, superior vena cava; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein. (Adopted from Armour JA, Murphy DA, Yuan BX, et al. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec.* 1997;247:289–298; and Pauza DH, Skripka V, Pauziene N, et al. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat Rec.* 2000;259:353–382.)

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but can be predictably sought in certain places during mapping (14,24). Several key areas have been identified to demonstrate a predominance of CFAE within our cohort: the proximal CS, the SVC–RA junction, the septal wall anterior to the right superior PV (RSPV) and right inferior PV (RIPV), the anterior wall medial to the left atrial appendage (LAA), the area between the LAA and the left superior PV (LSPV), and the posterosuperior wall medial to the LSPV (Fig. 11.4). Typically, patients with
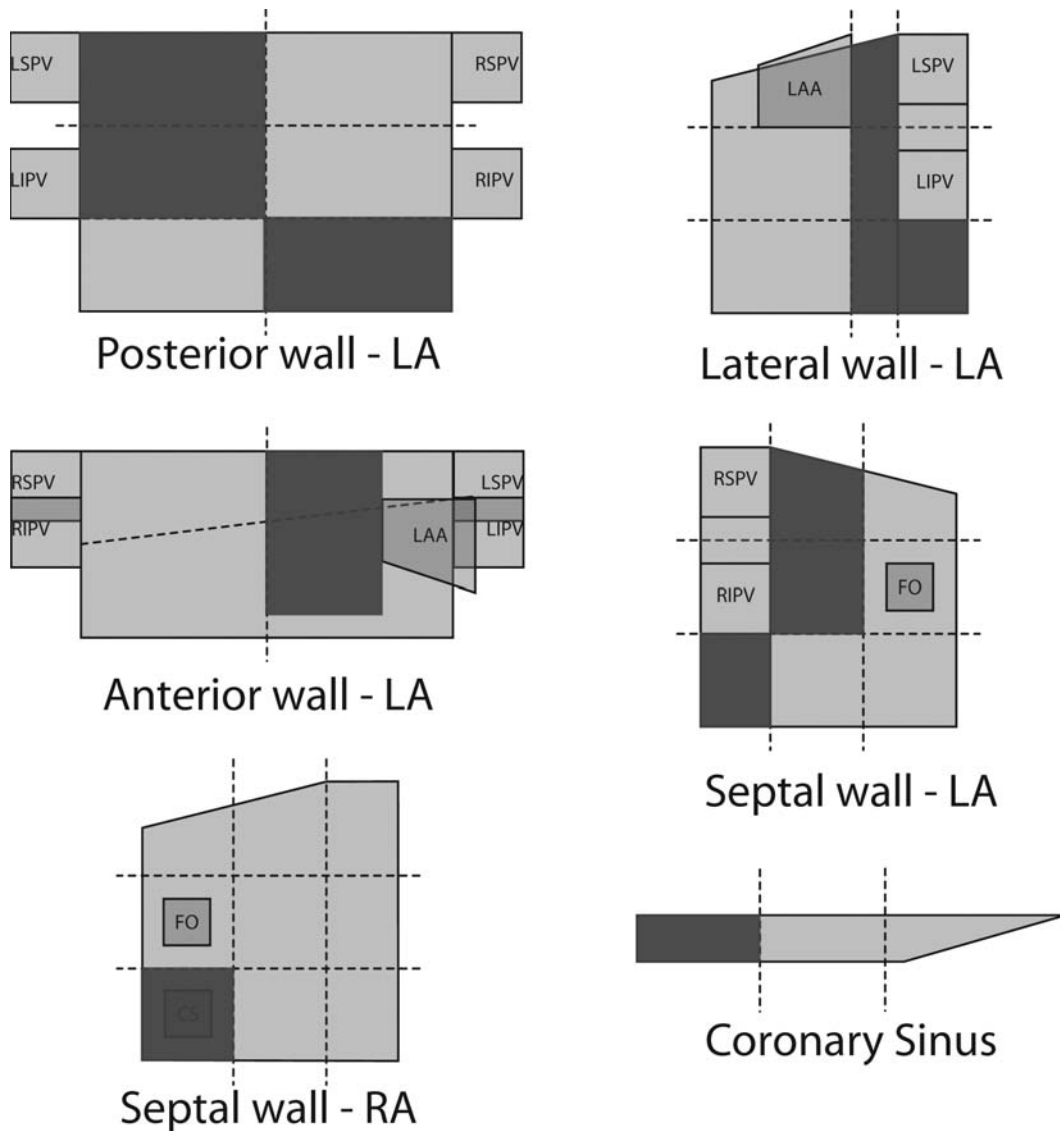
Figure 11.4. The most common locations of CFAE are identified (*darkest shading*) on a grid representing the regions of the right and left atria. LA, left atrium; LAA, left atrial appendage; RA, right atrium; CS, coronary sinus; FO, fossa ovalis; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

persistent or permanent AF have greater numbers and locations of sites with CFAE than those with paroxysmal AF (14).

Mapping Complex Fractionated Atrial Electrograms

Mapping always occurs during AF by point-to-point mapping, although it requires a very detailed electroanatomic map of the LA. The spatial and temporal stability of

CFAE has allowed the precise localization of these electrograms. We usually create a map with a minimum of 100 data points, especially in high density in areas commonly known to have CFAE. As well, we usually create a detailed map of the proximal CS, and occasionally the RA. We identify locations with stable electrograms and these are "tagged" to create targets for ablation. Areas with fleeting CFAE are not sought as a primary target. A highly reliable map allows for minimal use of fluoroscopy: We routinely use less than 10 minutes during an average procedure duration of 113 ± 27 minutes.

Recently we have developed and tested a customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA). The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-second recording window and interprets it according to two variables: (a) shortest complex interval (SCL) minus the shortest interval found (in ms), out of all intervals identified between consecutive CFAE complexes; and (b) interval confidence level (ICL) minus the number of intervals identified between consecutive complexes identified as CFAE, where the assumption is that the more complex intervals that are recorded—that is, the more repetitions in a given time duration—the more confident the categorization of CFAE. Information from these variables is projected on the 3-D electroanatomic shell according to a color-coded scale. This allows targeting and retargeting of areas of significant CFAE.

Procedural Details

A decapolar catheter is placed in the CS for reference and pacing. A single transseptal puncture under hemodynamic and fluoroscopic guidance is used to access the LA. Patients who are not in AF at the onset of the procedure undergo an aggressive induction protocol utilizing burst pacing in the CS and atria at a lower limit of 1:1 capture or $\approx$170 ms with additional intravenous isoproterenol (1–3 mcg/min) as required. AF is considered stable for mapping if it can be sustained for less than 30 seconds.

We use an open-irrigation 3.5-mm-tip ablation catheter with a large or extra-large curve (Thermacool F or J, Biosense-Webster) irrigating at 30 mL/min during lesion creation. Power settings are 35 to 45 W throughout the atria except for the posterior wall (15–30 W) and CS (10–25 W). Careful power titration is required during RF to ensure complete lesion creation. RF duration is usually 10 to 60 seconds and is halted because of patient discomfort or elimination of CFAE. Because of occasional noise on the ablation catheter during RF, multiple short (15- to 30-second) applications may be used.

One of the most important aspects of CFAE ablation (and one of the most common challenges early in the learning curve of this technique) is to revisit areas that were initially ablated to ensure that there has been no recovery of electrical activity. If the patient remains in AF despite elimination of all visible CFAE, intravenous ibutilide (1 mg over 10 minutes; may repeat once to maximum of 2 mg) is used to increase the cycle length of the arrhythmia in "nondriver" atrial tissue and thus highlight the remaining areas of greatest significance (e.g., CFAE associated with
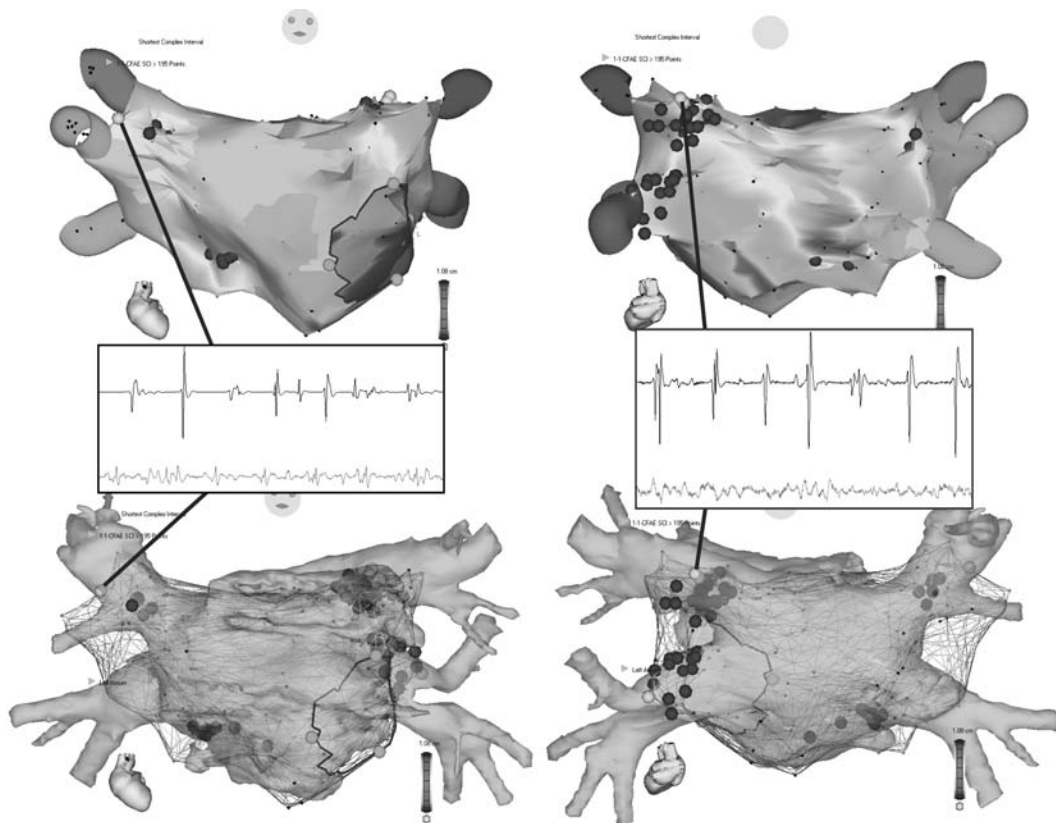
Figure 11.5. A CARTO 3-D electroanatomic map and a CARTOMERGE CT integration (Biosense-Webster) are shown demonstrating the location of the 18 lesions used to successfully treat a 36-year-old man with paroxysmal AF (left side, antero-posterior view; right side, postero-anterior view). Highly fractionated electrograms were located as depicted in the figure. Lesions were placed in antrums of the LSPV, LIPV, and RSPV, as well as the area between the LSPV and LAA, and the area anterior to the RIPV.

perpetuating AF). Alternatively, an intravenous dose of procainamide at 1,000 mg given as 20 mg/min may be used.

Often during CFAE-targeted AF ablation, the arrhythmia evolves into an AT. Using the CS catheter as a reference, the AT is subsequently mapped and ablated. Most often the sites of origin of the AT are at the same locations as the CFAE, which were targeted during the initial part of the procedure.

The endpoints employed are either: (a) termination of AF (and if the presenting rhythm was paroxysmal AF it must not be reinducible); or (b) elimination of all CFAE. Occasionally a patient will remain in AF or AT after an extensive ablation eliminating all CFAE and despite the use of ibutilide. In this small group of patients an external cardioversion is required.

In Figure 11.5, one can see an example of a 36-year-old man who underwent CFAE-targeted ablation for paroxysmal AF of 18 months duration. His only risk factor for AF is hypertension and he had not tried any antiarrhythmic drugs. His ejection fraction (EF) was 70% and his LA diameter was 41mm. AF was induced in the EP lab and was terminated with ablation. His procedure lasted 121 minutes
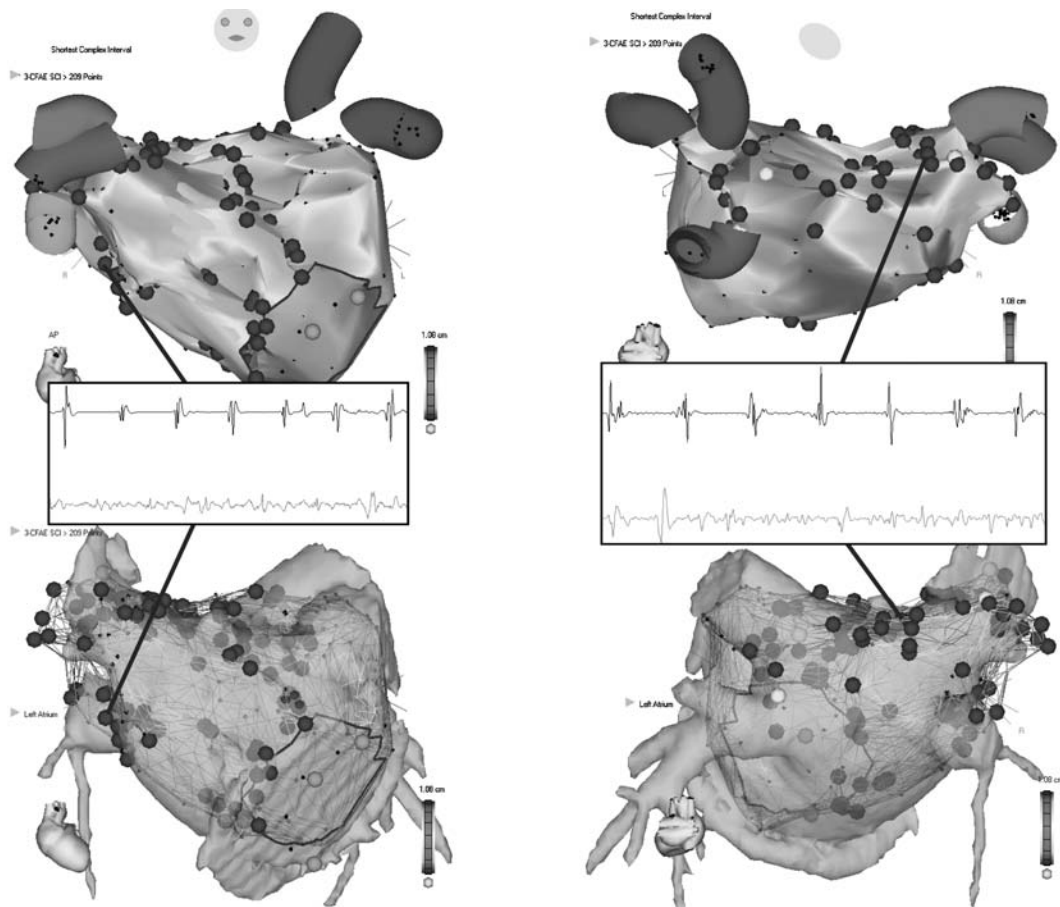
Figure 11.6. Despite the more heterogeneous distribution of CFAE seen on the CARTO and CARTOMERGE maps of this 68-year-old man with persistent AF, his AF was terminated during ablation without the need for ibutilide or cardioversion (left side, antero-posterior view; right side, postero-anterior view).

and required only 6 minutes of fluoroscopy. He required only 18 lesions (total RF duration of 15 min), which were localized to the antrums of the LSPV, LIPV, and RSPV, as well as the area between the LSPV and LAA, and the area anterior to the RIPV. One year following his procedure, he has had no further AF and is off anticoagulation.

An example of a CFAE-targeted AF ablation for permanent AF can be seen in Figure 11.6. The patient is a 68-year-old diabetic man with a 6-month history of persistent AF. His EF was 62% and LA diameter was 33 mm. His procedure was 115 minutes with 5:42 minutes of fluoroscopy and he required 71 lesions throughout the LA and CS (total RF duration of 30 minutes). The map demonstrates the significantly more complex nature of CFAE-targeted AF ablation in persistent AF when compared with the paroxysmal AF ablation seen in Figure 11.5. Nine months following his initial procedure, the patient remains in normal sinus rhythm and off oral anticoagulation.

Outcomes

Data from our lab targeting CFAE on 121 patients have been previously published and demonstrated a high success rate—91% symptom-free and without documented AF at one-year follow-up (14). Our cohort now encompasses 302 patients (69% male; mean age 62 ± 13 years) comprised of 47% paroxysmal AF and 53% chronic AF. Mean duration of AF is 5 ± 4 years and most patients had tried and failed at least two antiarrhythmic medications. Structural heart disease was present in 62%. Figure 11.7 shows the acute procedural outcomes stratified by type of AF: 83% of paroxysmal AF and 58% of chronic AF converted during AF ablation; the remaining patients required either ibutilide augmentation or ibutilide and cardioversion. One-year outcomes for paroxysmal AF can be seen in Figure 11.8 and for chronic AF in Figure 11.9. Of the 141 paroxysmal AF patients, 91% had no recurrence of AF (although 10% required antiarrhythmic drugs) and of the 161 patients with chronic AF, 85% were arrhythmia-free (despite antiarrhythmics in 18%). Seventy percent of paroxysmal AF patients and 66% of chronic AF patients required only one procedure, but many patients required two or three procedures.

Half of our cohort developed an atrial tachydysrhythmia after ablation. However, the majority were self-limited with 68% resolving within 12 weeks of the procedure. Of the 55 patients whose arrhythmias persisted, 46 underwent a repeat procedure. At the time of repeat ablation, 15 patients were found to have atypical left atrial flutters, 12 had typical cavotricuspid isthmus–dependent flutter, 11 patients had an atrial tachycardia (origins included the LSPV, RSPV, SVC, and CS os), and 8 patients are recurrent AF.

The origin of the atrial tachydysrhythmia is likely multifactorial. Tissue injury and healing may affect local electrophysiologic properties of the atria, as is commonly
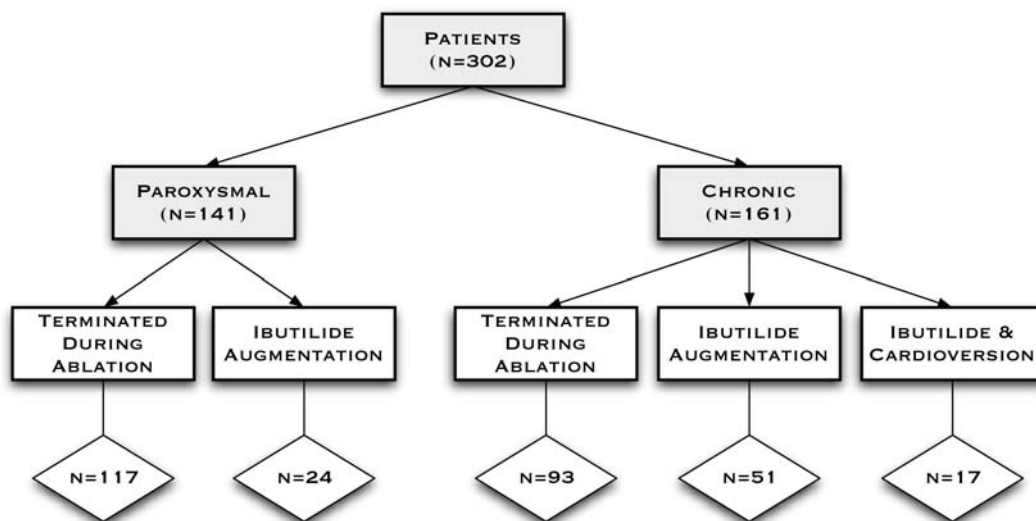

Figure 11.7. Our current cohort of AF ablation includes 141 patients with paroxysmal AF and 161 patients with chronic AF. All patients were returned to normal sinus rhythm at the conclusion of the procedure—83% of paroxysmal AF and 58% of chronic AF patients by ablation alone.
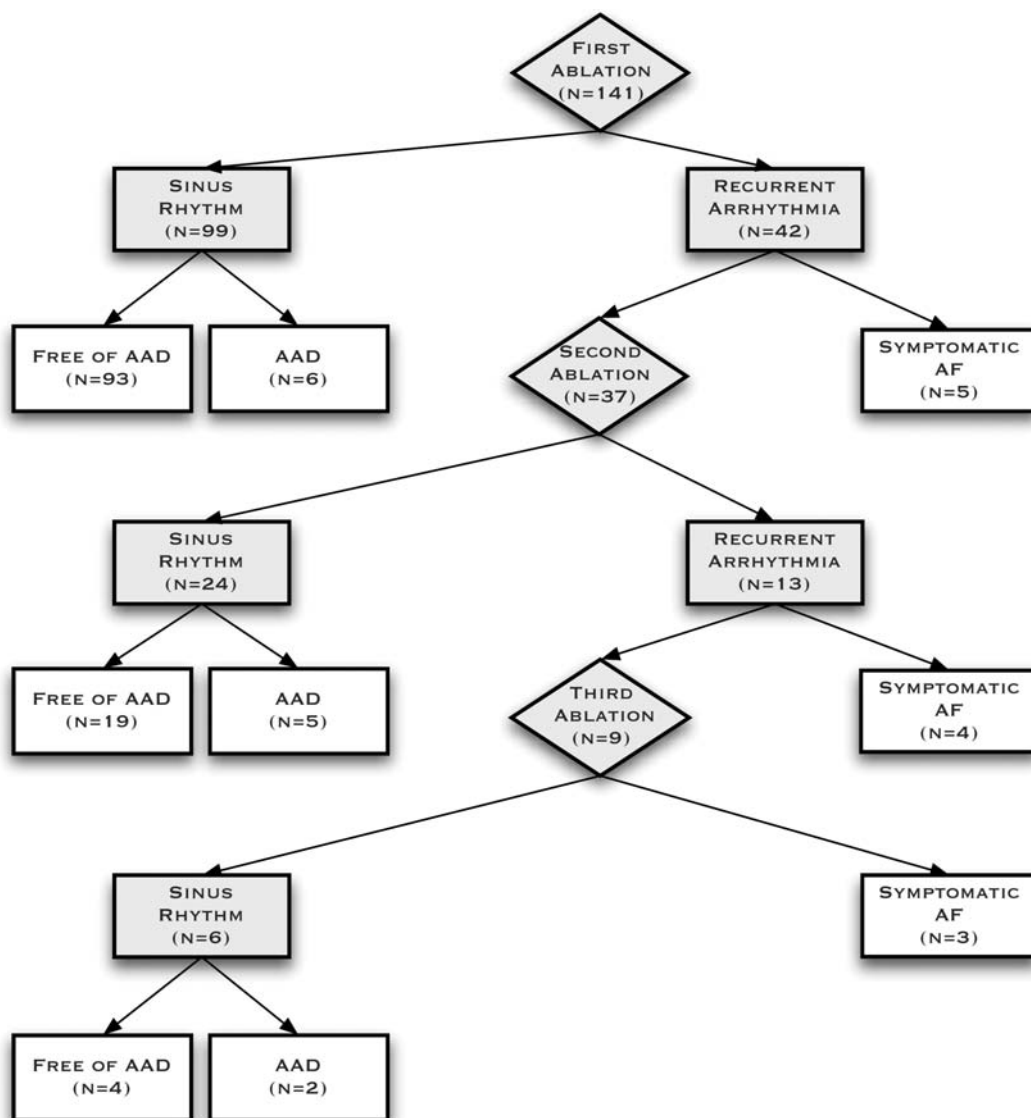
Figure 11.8. Of the 141 patients with paroxysmal AF, 91% were arrhythmia-free at one-year follow-up with only 10% on antiarrhythmics. However, 37 patients required a second procedure and nine required a third.

seen in a MAZE procedure (25). As one might expect with this theory, the arrhythmias resolve once healing is complete—approximately 12 weeks postprocedure. It is possible that the newly unmasked rhythm disturbance was the initiating arrhythmia for the AF in the first place. The third explanation for some of the arrhythmias is that the ablation lesions created the necessary milieu for the successful perpetuation of the arrhythmia, particularly the atypical left atrial flutters.

Major complications have been seen in 17 patients, including two cerebrovascular accidents, six with cardiac tamponade, one with complete AV block, and two with severe pulmonary edema. Six patients had complications related to vascular access including femoral arteriovenous fistula or pseudoaneurysm.
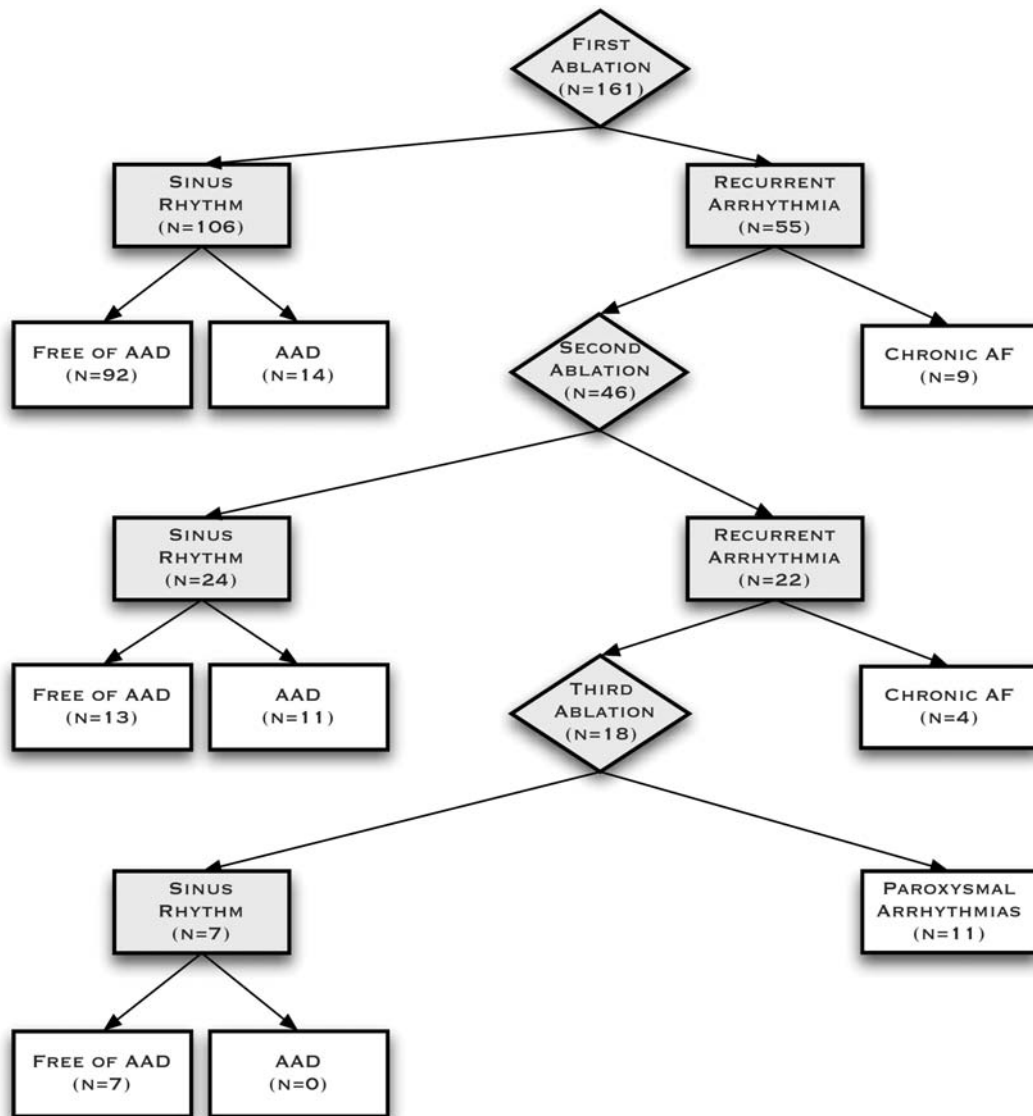
Figure 11.9. Eighty-five percent of the patients with chronic AF were arrhythmia-free at 1-year follow-up, but 18% required antiarrhythmics. Forty-six patients had two procedures and of those, 18 had a third.

Conclusion

Substrate modification is the cornerstone of our technique and the areas that we target consistently demonstrate evidence of stable complex fractionated atrial electrograms. Ongoing research into the true etiology of these electrograms will hopefully provide us with further explanation and understanding. Regardless of their etiology, we have demonstrated that a CFAE-targeted approach to ablation is very successful in the long-term treatment of AF.

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