Capnographic Observations during Cryoballoon Ablation of Atrial Fibrillation

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ABSTRACT. Background/Purpose: In the cryoballoon system, a continuous circumferential ablative lesion is created when there is complete occlusive contact between the cardiac tissue and balloon. A novel assessment of balloon occlusion can be made by monitoring end-tidal CO2 (etCO2) with a capnographic technique. Additionally, capnograms can be used as an adjunct to evaluate phrenic nerve function during the cryothermal ablation procedure.

Methods/Materials: During 20 cryoballoon cryoablation procedures, a quantitative capnographic protocol was introduced to assess the technique and determine the ability to gauge cryoballoon-to-pulmonary vein (PV) occlusion, and to monitor right phrenic nerve function.

Results: Monitoring etCO2 proved to be useful for assessing cryoballoon occlusion of PVs with a statistically meaningful decline in expired CO2 observed during ablation of all four PVs. Declines of 15.9%, 22.8%, 4.7%, and 5.7% were measured in the left superior PV, right superior PV, left inferior PV, and right inferior PV, respectively. The superior PVs had the most significant changes. This methodology can also be used as an additional monitor for early detection of phrenic nerve injury, but it should not be employed as the sole monitoring system for phrenic nerve dysfunction.

Conclusions: Capnographic measurement of etCO2 can be used successfully to monitor cryoballoon-to-PV occlusion while also potentially providing an early warning indicator of phrenic nerve injury during a cryoablation procedure.

KEYWORDS. atrial fibrillation, capnograph, cryoballoon, end-tidal CO2, phrenic nerve injury.

Introduction

The cryoballoon has emerged as an important, established, and approved system for the treatment of patients with paroxysmal atrial fibrillation (PAF).1–3 When occlusive circumferential contact is established at the pulmonary vein (PV) ostium, the cryoballoon creates durable PV isolation (PVI).4 PV occlusion is verified by injecting radiopaque contrast agent through the nose of the cryoballoon and observing the retention of contrast agent in the distal PV branches by fluoroscopy.5 Additional methods (for PV occlusion testing) have included PV pressure waveform monitoring6 and intracardiac echocardiography (ICE) examination under Doppler flow display.7 In this study, the primary aim is to describe and quantify capnographic changes during cryoballoon PV ablation, and to determine the utility of end-tidal CO2 (etCO2) as a novel indicator of PV occlusion during ablation. The secondary aim is to assess the ability of capnograms to detect early right phrenic nerve dysfunction. The rate of procedural phrenic nerve injury (PNI) has declined between STOP AF (11.2%; NCT 00523978) and STOP AF PAS (3.1%; NCT 01456949), but there is need for an early warning system for impending phrenic nerve impairment, interruption, and/or damage.2,3 A widely used technique is to pace the right phrenic nerve electrically during right-sided PV ablations,7 and to assess nerve integrity manually by palpation. Monitoring the amplitude of the diaphragmatic compound motor action potentials (CMAPs) via electromyograms is another
promising technique. In other clinical usages, diaphragmatic activity has been capnographically detected, and it may be possible for capnograms to detect early PNI.

Material and methods

Observations were made on 20 patients with PAF undergoing PVI with the cryoballoon ablation system (Arctic Front Cardiac CryoAblation Catheter; Medtronic, Inc., Minneapolis, MN). The collection of capnographic data during clinically indicated procedures was approved by a patient consent waiver, and the study was approved by the local hospital institutional review board.

Patient characteristics

The 20 subjects had similar inclusion criteria to those enrolled in the STOP AF trial. Study enrollment included 12 males and 8 females with a mean age of 68 years (± 9.3 SD; ± 2.1 SEM; range 58–81). All patients had symptomatic PAF and a documented recurrence of AF despite one or more attempts at antiarrhythmic drug therapy. Every patient was in normal sinus rhythm at the start of the ablation procedure. Two patients had pacemakers, and 1 had an implantable loop recorder. This was the first AF ablation procedure in all 20 patients.

Capnogram technique

The capnography technique measures the concentration of CO2 in exhaled gas by sidestream gas sampling, and is used extensively during general anesthesia. Capnographic equipment uses infrared technology to detect CO2, and capnography is utilized to monitor the adequacy of systemic, pulmonary, and coronary blood flow. During capnographic monitoring, cardiac output and etCO2 have a logarithmic relationship; consequently, capnographic assessment of etCO2 is a sensitive indicator of pulmonary blood flow. In this study, the relationship between etCO2 and PV blood flow is used as a potential marker for the ventilation-perfusion mismatch created by the cryoballoon occlusion of a PV during cryoablation. During this study, patients were placed under general anesthesia and ventilated via the endotracheal route using a volume control mode. The capnographic waveform and etCO2 (derived from the infrared detector via sidestream gas sampling) were monitored continuously throughout the ablation procedure with an anesthesia machine (Draeger Fabius Tiro; Drägerwerk AG & Co., Telford, PA). A snapshot of the data screen displaying continuous etCO2 waveforms was automatically recorded every 5 s using a computer with video capture ability (Figures 1 and 2). The etCO2 was tabulated at pre-ablation baseline and every 60 s thereafter during each 240-s cryothermal ablation application with the cryoballoon catheter (Figure 3).

AF ablation

In all 20 patients, electroanatomical voltage maps of the left atrium and PVs were obtained before and after the ablation procedure to verify PVI along with entrance and exit block testing. All patients had conventional four-PV anatomy with no left common or anomalous veins, and all 80 PVs were ablated with the cryoballoon catheter only. Balloon sizes were 28 mm in 16 patients and 23 mm in 4 patients. The cryoballoon ablation procedure has been described extensively in other publications; thus, the description given here is brief. During this study, the standard cryoballoon freeze dose was a 240 s ablation followed by another 240 s ablation in a freeze-thaw-freeze method. The cryoballoon ablation application was terminated earlier than 240 s if a decrease in right phrenic nerve function was detected, or if a 10°C drop was noted with an esophageal temperature probe. In this study, all 80 PVs were acutely isolated with the cryoballoon, and persistence of isolation was confirmed by repeat testing at the conclusion of the ablation procedure.

Capnogram versus CMAP

Additional qualitative observations were made relating the capnographic waveforms to the CMAPs in patients with transient right phrenic nerve impairment during ablation (Figure 4), and during the assessment of the phrenic nerve stimulation threshold(s) prior to ablation (Figure 5). These observations were recorded in a qualitative observational format, after the initial 20-patient study, as the value of CMAP monitoring became more evident.

![Figure 1: Capnographic changes during AF. (a) Baseline etCO₂ of 32 mm Hg. (b) After occlusion, etCO₂ declines to 25 mm Hg and reaches a final nadir etCO₂ at 21 mm Hg. (c) Phrenic nerve stimulation is observed as notches (white arrow). Note the lag-time between initiation of phrenic stimulation (asterisk) and appearance of notches (white arrow). (d) Prompt recovery to baseline etCO₂ (32 mm Hg) following balloon deflation.](image-url)
Statistical analysis

The differences in the pre-ablation baseline etCO₂ compared to the 2-min etCO₂ (during cryoballoon ablation) were evaluated for each of the four PVs in all 20 patients using a two-tailed Student’s t-test, and statistical significance was set at p < 0.05 (Figure 3). All data points in Figure 3 are mean values of the initial 20 patients’ measurements of etCO₂, and error bars are recorded as ± one standard error of the mean. Statistical evaluations of etCO₂ were conducted between baseline (0 s) and 120 s because maximal decline in etCO₂ occurred between these two time periods during cryoballoon ablation; typically, most etCO₂ falloff was attained within 20 s of achieving a contrast-verified occlusive balloon position.

Sensitivity for the capnographic assessment of occlusion was assessed by the presence of a decrease in the etCO₂ value at 1 min of ablation, compared to the pre-ablation baseline. Specificity could not be assessed directly in this protocol, since the criterion for initiation of cryoablation was PV occlusion demonstrated by contrast retention. However, when contrast retention balloon occlusion testing demonstrated non-occlusion by the presence of a leak, we also did not observe any decline in the etCO₂ measurement.

Results

The sidestream etCO₂ gas sampling method inherently introduced a 3–4 s lag-time from the actual gas sample.
collection until the capnogram display. During the cryoballoon positioning at either the left superior PV or the right superior PV, there was typically an easily appreciated decrease in etCO₂ after complete venous occlusion proven by venography. Sensitivity was 90% for the right superior PV, and 70% for the left superior PV. The technique is much less sensitive for the inferior veins, at 50% for both the left inferior PV and right inferior PV. In all 20 patients, all 80 PVs were successfully occluded and isolated by cryoballoon application.

**Capnogram detection of occlusion**

Typical capnograms for cryoballoon occlusion of the right superior PV are shown in Figure 1. The electrocardiogram (EKG) sweep speed is 25 mm/sec, and the capnogram sweep is 6.25 mm/s. After cryoballoon occlusion, the etCO₂ declines from a baseline of 32 mm Hg (Figure 1a) to 25 mm Hg (Figure 1b) and then to a nadir of 21 mm Hg (Figure 1c). Note the lag-time from onset of phrenic stimulation artifact on surface EKG to the appearance of a phrenic notch (asterisk to arrow in Figure 1c). Rapid recovery of the etCO₂ follows balloon deflation (Figure 1d).

In this right superior PV example, there were no cardiogenic oscillations present in the (phase III) expiratory plateaus; however, the decline of etCO₂ confirmed occlusion. During diaphragmatic contractions induced by right phrenic nerve electrical pacing, there was a reproducible notch in the etCO₂ waveform (arrow in Figure 1c) that was analogous to the “curare cleft” or “breathlets” seen with spontaneous diaphragmatic movements in unparalyzed patients during general anesthesia.10,18

Cardiogenic oscillations are well described in the capnographic literature,13–16 and represent small fluctuations in the CO₂ waveform related to minor displacements of lung volume produced by cyclic cardiac motion (demonstrated in Figure 2). Figure 2a and b depict a left inferior PV with the onset of cardiogenic oscillation during cryoballoon occlusion (arrow in (a)); 30 s later, (b) shows phasic cardiogenic oscillations that are fully developed, which is also characteristic for balloon occlusion, even though the mean etCO₂ declined only slightly to 33 mm Hg. During AF, the onset of right superior PV occlusion is shown in Figure 2c, with simultaneous decline of etCO₂ and onset of cardiogenic oscillations, which are fully developed 30 s later in (d). Although the oscillations are random during AF, their presence also seems to confirm an occlusive balloon position, and in this example, the balloon occlusion was also confirmed by a decline of the etCO₂.

The presence of AF without distinct A and V waves did not limit the ability of cardiogenic oscillations to predict occlusion.

In Figure 3, the graphical data show the significant decline in mean etCO₂ that was detected in all PVs amongst the 20 patients studied. The left superior PV etCO₂ measurement decreased by 15.9% and the right superior PV declined by 22.8%. Similarly, there was a statistically significant decline of 4.7% in the left inferior PV etCO₂ measurement from baseline, and 5.7% change in the right inferior PV. All four PVs demonstrated a
consistent etCO₂ nadir measurement at the 2 min post-ablation time point. Comparing all PVs, a more substantial change in the mean etCO₂ was observed for the superior PVs (Figure 3); however, characteristic development of cardiogenic oscillations was another indicator of cryoballoon-to-PV occlusion that was easily appreciated, even in the absence of major decline in the mean etCO₂ (Figure 2). The cryoballoon may transfer atrial motion or pressure to the lung, resulting in small displacements of CO₂ and resulting in oscillations. In this study, every effort was made to maintain a proximal occlusive cryoballoon position at the external ostium of each PV. However, inherent differences (in cooling efficiency related to PV diameter and flow) influence the transfer of cardiac motion to the adjacent lung tissue, and likely explain the variability we observed in the appearance of cardiogenic oscillations.

**Capnogram detection of PNI**

A qualitative assessment of an additional 50 patients was conducted to examine the utility of PNI detection with capnography. During early phrenic nerve impairment, the amplitude of the notch could rapidly decline, despite continued palpable diaphragmatic contractions; thus, it provided an early indication of partial PNI (Figure 4). This was confirmed with the simultaneous display of the CMAP (Figure 4). Upon phrenic recovery, a strong palpable diaphragmatic contraction could be felt well before a reappearance of the notch in the etCO₂ waveform. These observations suggest that the maximal baseline notching occurs only with full diaphragmatic excursions, and that the notch declines and disappears with attenuated contractions, resulting in less lung volume change. Additional evidence linking the amplitude of the phrenic notch to right diaphragmatic function is shown in Figure 5. During evaluation of phrenic nerve stimulation prior to ablation, the stimulus strength is varied with a corresponding decline in the CMAP. At 12 ma, the amplitude of CMAP is decreased to approximately 70% of baseline, whereas the phrenic notch amplitude is at 30% of baseline amplitude. At 7 ma, the CMAP is reduced to 40% of baseline, and the phrenic notch is barely detectable (arrows; Figure 5c). Lastly, the bottom panel shows the capnogram in the absence of any phrenic stimulation.

**Discussion**

Capnographic monitoring is a standard method for real-time assessment of cardiopulmonary function during a general anesthesia procedure. This study is the first reporting of capnographic monitoring to assess cryoballoon occlusion of PVs during cryoablation, and it establishes the quantitative magnitude of changes in the etCO₂ that is typically observed during a cryoballoon ablation procedure. The data demonstrate that the PV-location-dependent changes that occurred in etCO₂ are highly sensitive for cryoballoon occlusion for the superior PVs. In contrast, the etCO₂ is a less sensitive indicator for occlusion of the inferior veins, although the development of cardiogenic oscillations may be an additional indicator of balloon occlusion. The differences between the superior and inferior PVs may reflect a higher proportion of gas exchange occurring in the upper lobes during general anesthesia. Specifically, under volume control ventilation, the anesthesiologists are conservative in their choice of tidal volume to avoid hyperinflation and barotrauma. Consequently, the lower lobes are systematically under-ventilated; thus, the impact of a ventilation–perfusion mismatch in the lower lobes is not as obvious by capnogram detection in this study.

Due to the slower time course of capnographic confirmation of occlusion compared to other methods, we do not advocate use of the capnogram as the primary modality to verify balloon occlusion. In select cases, we have successfully relied on the capnographic technique exclusively, to avoid or minimize contrast agent administration (in patients with renal dysfunction or pre-diagnosed radiopaque contrast agent allergies). When used as the secondary modality to assess occlusion, the capnogram is readily available and is useful mostly as a confirmatory indicator of continued full PV occlusion. For example, the capnogram can reveal dislodgement of the balloon occurring after contrast agent injection (but before full cryoballoon freeze-adherence to cardiac tissue), or after the pressure waveform guidance is lost by freezing of the guidewire lumen within the cryoballoon catheter. We have also worked with obese patients in whom fluoroscopic visualization of contrast is difficult, and in whom the capnographic confirmation of occlusion was quite helpful. Fluoroscopic visualization of the PVs during contrast agent occlusion testing can be difficult in severely obese patients because of the reduction in fluoroscopy penetration across a larger body mass, and instead of exposing these patients to a larger radiation dose, a capnogram technique can also be used to help assess balloon-to-PV occlusion.

Also, the cryoballoon ablation procedure routinely involves multiple cryothermal energy applications, and a promising utility for capnographic monitoring is with cryoballoon repositioning for repeat ablation applications. After an initial ablation with occlusion verified by contrast injection, the characteristic capnographic waveform changes were sufficient to repeat occlusion of the same PV for a second "re-freeze" ablation, without additional usage of contrast agent, ICE imaging, or fluoroscopy. The cryoballoon nadir temperatures and rewarming times that were achieved on the repeat ablations were comparable to the initial ablation application (with occlusion verification by contrast agent and fluoroscopy). Recovery of the capnographic waveform to baseline after balloon deflation heralds the onset of transient hypotension, which is routinely observed, and it can prompt an evaluation for loss of balloon adherence and the ability to reposition the cryoballoon catheter safely.

In comparison to other methods of pre-ablation assessment of cryoballoon occlusion, the etCO₂ monitoring method was also reliable during AF. This differs from the pressure monitoring technique, which is not as reliable.
during AF because of the absence of distinct A and V waves. Additionally, ultrasound-Doppler visualization of the right superior PV can be difficult during an ablation procedure; however, this PV shows the most dramatic and consistent etCO2 changes during cryoballoon occlusion.

Alterations of the etCO2 can indicate an impairment of the pulmonary gas exchange, blood flow, and ventilation. The changes described during the cryoballoon occlusion procedure should not be confused with these other causes that are consistent with acute intraprocedural decline in etCO2. The technique described in this study is limited to cryoballoon ablation procedures performed under general anesthesia. The etCO2 and capnographic waveform is readily available for display during such cases, and does not require any additional special technology, making this method easily adoptable within any existing anesthesia monitoring system utilizing correct capnographic methodology.

The amplitude of the notch in the expiratory plateau phase of the etCO2 waveform during phrenic nerve electrical pacing was proportionate to the intensity of palpable diaphragmatic contractions and the amplitude of the CMAP. Considering experience gained with all three methods in the qualitative observational study (CMAP, manual palpation, and capnogram), we believe that the CMAP is overall a more reliable method for monitoring diaphragmatic contractions induced by high-current-strength right phrenic nerve stimulation. The capnographic method of phrenic nerve monitoring is useful as an additional marker for the early detection of right phrenic nerve injury, and it can be used when the CMAP signal is inadequate. For instance, in severely obese patients, reliable CMAP recordings can be difficult to obtain because of electrical attenuation across a larger body surface area. Additionally, even the correct placement of CMAP recording electrodes can be distorted in an obese patient, and in this situation, the added usage of capnographic evidence may be particularly helpful since it is a direct measure of pulmonary gas exchange, independent of body mass. However, manual palpation and CMAP assessment(s) should be attempted first in every case.

**Limitations**

The observations of the capnographic detection of PNI were qualitative assessments; however, it was readily apparent that the capnogram method would not be a single monitoring system that could replace CMAP or manual detection of phrenic nerve dysfunction. Consequently, a prospective quantitative assessment was not conducted. Only a sidestream capnogram sampling method was used in this study, and it is generally well accepted that a mainstream capnogram sampling will have a shorter lag-time of reporting. However, it is not known how much the lag-time will decrease in this method, and there are several variables that will need to be considered in each laboratory, including length and diameter of sampling tubes. Lastly, the patient population size in this series of examinations was small; however, the primary intent of this manuscript is the simple introduction of a new technique that may be considered in clinical decision making when using the cryoballoon catheter.

**Conclusion**

The capnographic waveform and etCO2 can be utilized in patients under general anesthesia as an additional technique to monitor cryoballoon-to-PV occlusion while also potentially aiding in detecting early and reversible PNI during a cryoablation procedure. This methodology may be used to enhance current protocols during cryoballoon ablation procedures, and it requires minimal additional equipment.

**References**


