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Novel Dye-less and Fluoro-less Approach to Cryoballoon Pulmonary Vein Occlusion Assessment

Short Title**: Dye-less Pulmonary Vein Occlusion**

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Abstract

Background: Occlusion of pulmonary veins is essential for PV isolation using the Cryo balloon. Currently occlusion is arbitrarily determined using fluoroscopy and contrast media. This study aimed to create an objective measure without utilizing excessive fluoroscopy and no contrast media.

Objective: Ensure PV occlusion without fluoroscopy and contrast dye.

Methods: In 4 in vivo hearts 113 PV occlusions were tested with a 50% cold dye saline mix at 4°C. Occlusions were rated "Good", "Fair", and "Poor" by dye dissipation seen via fluoroscopy and correlated to temperature profiles recorded concurrently. Using these temperature profiles and no dye, cryoablations were placed in 12 additional hearts (56 unique veins, 126 occlusions). Two 180 sec cryo applications were placed per vein with occlusion testing in-between. PV isolation was defined by EP mapping, gross pathology and histology after ≥4 weeks recovery.

Results (dye): With "Good", "Fair" and "Poor" the maximal post injection PV temp dropped (ΔT) by 6.2±4.2, 5.1±3.7, and 2.4±2.0°C. At 5 sec post nadir temperature of injection temperature recovered 18±14%, 36±23, 50±33%. Console thaw time to 0˚ C was 11.5±4.8, 8.5±2.1, 4.3±1.3 sec. Success rate for PVI was 100, 97 and 0%.

Results (no dye); ΔT: 7.7±4.4, 5.8±5.0, and 3.4±2.3°C, % recovery at 5 sec: 15±12, 31±23, 45±30%, Thaw time to 0°C: 11.9±4.8, 10.5±5.2, 6.0±2.8 sec, Success rate was 97, 91 and 10%.

Conclusion: PV occlusion profile determination using 4°C cold saline injection is an effective approach to define the occlusion grade. Quality occlusions correlate strongly with PVI success.

5 key words: Pulmonary vein isolation, cryoballoon, occlusion, ablation, atrial fibrillation

Introduction

A fundamental requirement of achieving a durable pulmonary vein isolation (PVI) using the Cryoballoon technology is pulmonary vein (PV) occlusion prior to the initiation of the freeze cycle.[1] Occlusion is defined as pressing the anterior sections of the balloon against the circumferential base of a vein, to obstruct blood flow from this vein. A proper ("good") occlusion results in complete blood obstruction, Circumferential and pulmonary vein (PV) isolation (PVI). A improper ("poor") occlusion results in blood flow over a section of the Cryoballoon preventing circumferential ablation of the PV. These segmentally ablated veins require balloon repositioning and additional ablations to achieve total isolation, thus increasing procedure time and the possibility of complications. The expected result of undetected segmental ablations is PVI failure and increased likelihood of AF recurrence.

Currently, to determine the degree of occlusion, dye is injected into the vein via the balloon catheter central lumen. This is done while the balloon is inflated and positioned to occlude the vein. This subjective approach, while being deemed acceptable, still requires both dye and fluoroscopy.[2] Fluoroscopy and contrast dye, however, can be harmful for patients. Contrast media, in particular, can be difficult to manage for patients suffering from renal dysfunction. A reduction of both fluoroscopy and contrast dye is desirable.

In this investigation, we report an objective technique that replaces the need for fluoroscopy and dye injection. This technique aims to define proper occlusion, which translates into successful, circumferential ablation of veins.[1,3] A prototype based on the Arctic Front Advance Cryoballoon catheter design (Medtronic, Minneapolis, MN) was instrumented with a temperature sensor ring placed on the shaft just distal to the balloon anterior surface (Figure 1). We hypothesized that if the PV is properly occluded, injecting 5cc of 4°C cold saline via the balloon central lumen will

result in marked temperature drop and slow rewarming obviating the need for both radio-opaque dye and fluoroscopy.

Methods

All procedures were performed in compliance with the American Heart Association's guidelines for animal research and approved by the Animal Care Committee of the University of Illinois at Chicago. Canines (30-35 kg) underwent anesthesia induction with intravenous propofol (0.5 mg/kg) and maintenance with inhaled isoflurane 1.00-1.75% via endotracheal intubation. Intra-arterial blood pressure and esophageal temperature monitoring were performed throughout the entire experimental protocol and core temperature was maintained at 38.0±1.3˚C using a heating blanket.

A 20-pole deflectable catheter was inserted into the external jugular vein and positioned in the high right atrium extending into the coronary sinus.

Using fluoroscopic and transesophageal echocardiographic guidance, trans-septal puncture was performed and a 14F deflectable delivery sheath based on the Flexcath design (Medtronic, Minneapolis, MN) was inserted into the left atrium (LA). Prior to insertion of the Cryoballoon, the chamber anatomy, PV orifices, and LA voltage maps were generated using a 20-pole deflectable catheter and the EnSite NavX 3D (St. Jude Medical, St. Paul, MN) navigation system. A 0.035" guide wire was advanced into the targeted vein and a 23 or 28mm Cryoballoon was inserted and positioned to engage the PV. The balloon size was selected based on the PV orifice size.[1]

In this animal model, the 23mm balloon was sufficient for most veins, but a 28mm balloon was necessary for the right superior vein. The investigation consisted of two phases. In phase one,

the occlusion was assessed using 5cc of a 50% dye/saline mix chilled to 4°C injected into the targeted PV. For each injection, both the contrast dye and saline solutions were chilled separately to 4°C and mixed just prior to the procedure. The dye/saline mix was then chilled in an ice bath throughout the procedure. The dye dissipation time and the temperature from the distal ring thermocouple were recorded simultaneously. In 4 hearts, 113 test occlusion runs were defined by dye dissipation rate. "Good" occlusion was defined by dye stasis and full vein opacification above the balloon, with slow dye dissipation rate. Dye persisted for in a range from 26-194 seconds with a mean of 67±45 seconds. This was associated with minimal change to visible density of dye during this period. "Fair" occlusion was defined by full vein opacification by dye that proceeds to dissipate post injection. This was defined as dye persistence in range between 7-33 seconds with a mean of 19±8.2. There was visible loss of dye density over this period. "Poor" occlusion was defined by visible dye injection that does not achieve vein opacification and dissipates rapidly post injection. Dye persistence was in a range from 0–8 seconds with a mean of 5±2. This was associated with rapid loss of visible dye density immediately upon injection.

Distal temperatures were measured alongside the cold dye/saline injection runs. Based on the profiles acquired in the first phase, the quality of the occlusion was assessed based on the temperature profile only in the second phase. Twelve (12) in vivo hearts had 126 test occlusions performed with 5cc 4°C saline injection only (no dye or fluoroscopy). In all hearts, each PV ostia underwent two 180 second freeze cycles that were associated with "Good", "Fair", or "Poor" occlusions.

The data parameters consisted of dye dissipation time (s), the lowest temperature post injection (°C), the change in temperature from baseline (Δ°C), and the percent recovery of the temperature 5 and 10 seconds post the nadir temperature (% Return at 5 and 10 sec). The ring electrode

temperature data from each occlusion and cryo application was correlated with the internal Cryoballoon temperature parameters that were used to analyze the quality of the freeze cycle. These parameters were: internal temperature at 60 seconds of freeze, the nadir temperature achieved, and the thaw time to 0°C. After 4 weeks of recovery PV isolation was defined by EP mapping, gross pathology with tetrazolium stain, and histology using trichrome staining.

Statistics

Analysis of variance was used to determine whether there were significant differences between mean values obtained from recordings for each of the occlusions. If the overall test for a variable was significant, comparisons were performed using Student's t-tests. All data are expressed as mean ± standard deviation. A 2-tailed p value of ≤ 0.05 was deemed significant.

The predictive capability of each occlusion level, as defined by the cold saline injection, was validated by the electrical mapping and histopathological analysis of the PVs ostia as well as the intra-balloon freeze characteristics.

Results

With “Good” occlusion, post injection of 4°C 50% dye/saline or only cold saline, the average ring thermocouple temperature decreased by 6.2±4.2°C with dye and 7.7±4.4°C without dye, followed by a slow rewarming phase of 18±14% and 15±12% at 5 seconds and 36±23% and 30±17% rewarming rate at 10 seconds. The “Fair” occlusion with cold dye/saline or only cold saline injection the temperature decreased 5.1±3.7°C and 5.8±5°C. The rewarming rate was 36±26% with dye and 31±23% without dye after 5 seconds and 58±24% and 48±26% rewarming rate at 10 seconds. The “Poor” occlusion with cold dye/saline or only cold saline injection decreased by 2.4±2°C and 3.4±2.3°C and rapidly re-warmed at a rate of 50±33% and 45±30% after 5 seconds and 70±25% and 61±28% rewarming rate at 10 seconds. There are no significant differences between dye and no dye values. However, for both dye and no dye, post injection temperature decrease and percent recovery at 5 and 10 seconds were significantly different between the three occlusion levels (Table 1, Figures 2, and 3). The temperature recovery curves post injection as shown in Figure 2 and 3 and are significantly different between each of the occlusion levels.

During the freeze cycle and thaw period the differences in internal balloon/console temperature profiles between each occlusion level shows significant discrimination between the “Good” vs. “Poor” and “Fair” vs. “Poor” with marginal discrimination capacities between “Good” and “Fair” (Figure 4 and Table 1). The success rate of the ring electrode temperature profile for predicting PVI post injection of 4°C 50% dye/saline or only cold saline cold respectively, was 100% (17/17 PV’s) and 97% (38/39 PV’s) for “Good” occlusion, and 82% (9/11 PV’s) and 91% (10/11 PV’s) for “Fair” occlusion. The ablation outcome with “poor” occlusion for post injection of 4°C 50% dye/saline or only cold saline was 0% (0/23 PV’s) and 10% (3/30 PV’s).

Post ablation tissue electrograms amplitude, PV electrical activity, and conduction were absent (voltages of ≤0.5 mV) in all "Good" occlusions and 10/11 of the "Fair" occlusions, but 27/30 PVs ablated with poor occlusion retained electrical activity post cryo application.

An example of the differences in gross pathology and the histology due to variable occlusion is shown in Figure 5. These occlusions were done in the same animal. The minimal temperature drop and rapid recovery demonstrating "Poor" occlusion versus the marked temperature drop and slow recovery associated with the "Good" occlusion is shown in Panel C. The tetrazolium stained PV tissue and the trichrome stain histology demonstrating a partial ablated orifice and a large gap of surviving tissues due to the partial occlusion (panel A). In contrast the "good" occlusion resulted in circumferential lesion with no surviving PV sleeve myocardium (panel B). The internal balloon temperature corroborates the pre-ablation "Good" and "Poor" occlusions (Panel D and E). No safety issues were encountered with this technique.

Discussion

The aim of this investigation was to determine whether the temperature profile of a thermocouple placed in front of the balloon and exposed to 5cc 4°C rapid cold saline infusion can discriminate between "Good", "Fair", and "Poor" PV occlusions. As noted with the dye injection, a "Good" PV occlusion result in dye stasis and prolonged dye dissipation that was associated with a temperature drop of 6.2±4.2°C and a slow temperature rewarming of 18±14% at 5 seconds. In contrast the poor occlusions the temperature declined by only 2.4±2°C and rapid rewarming of 50±33% at 5 sec. Similar results were documented with an injection of 5cc 4°C cold saline without the use of fluoroscopy. Validation of occlusion level defined by the cold saline injection was further confirmed by the internal balloon/console temperature profile during freezing. More impotently the "good" occlusions resulted in 97% PVIs, "fair" occlusion 91% PVI while "poor"

occlusions resulted in only 10% PVI. Although it is very unlikely that "poor" occlusion would result in circumferential PV lesion the buildup of ice during the freeze can in some cases seal the gap and lead to circumferential lesion formation.

In previous investigations, the direct pressure monitoring from the Cryoballoon central lumen was also found to be useful in detecting PV occlusion. This technique, however, is subjected to pressure waveform variations and changes associated with AF and phrenic pacing.[4]

As with the pressure monitoring, temperature monitoring from a thermocouple placed at the nose of the balloon is an effective approach to define the PV occlusion. This is accomplished by using only chilled 4°C cold saline that is injected into the targeted PV in the same manner as contrast dye. This approach allows quantification of the occlusion and greatly reduces the use of contrast dye and fluoroscopic exposure. Achieving a more consistent PV occlusion using this method will likely result in an increase of single ablation success and reduce the need for repeat freezes. By extension this will also decrease the possibility of extra-cardiac damage, such as phrenic nerve palsy or the formation of atrio-esophageal fistula.

Furthermore, this technology could be adapted to quantitate the efficacy of the occlusion within the Cryo console system. This would allow the console to alert the operator whether the PV occlusion is "Good" or "Poor" and whether cryo-ablation should be initiated. The lowest temperature drop post cold saline injection and the rate of rewarming recorded from the distal ring thermistor allows for a high degree of discrimination and confidence in the occlusion quality.

In clinical studies that resulted in successful PVI, the internal temperature during the freeze cycle achieved a nadir of ≤-48˚C and mean internal temperatures of ≤-40 ˚C at 60 sec.[5] Another study found that successful pulmonary vein isolation was associated with thaw durations to 0°C of

14.8±10 seconds. Veins that reconnected had thaw durations to 0°C of 7±2 seconds.[6] These clinical results are similar to our own. The failure to reach the internal balloon temperature profile associated with unsuccessful PVI is a result of "Poor" PV occlusion. Providing the operator with quantitative assessment of the PV occlusion may eliminate ineffective cryo-applications and more importantly may improve outcomes and eliminate the use of dye and fluoroscopy.

Limitations

The study is a proof of concept performed in an animal model. Human clinical trials will be needed. The injection of the cold saline will require saline reservoir maintained at constant temperature (we have accomplished this need by immersing the saline bag in a bucket of ice cubes and water) and a closed system with the appropriate air trap and safety measures to prevent any air from being injected directly into the heart.

Small, but notable differences between mixed dye/saline and saline-only injections are noted in the table. The dye/saline mixture is more viscous resulting in a slower injection rate. The slower injection rate is likely the reason for the warmer nadir temperatures and slightly faster recovery.

Conclusion

The prototype Arctic Front Advance Cryoballoon catheter was instrumented with a temperature sensor ring placed just distal from the balloon anterior surface. The temperature profile recorded from the thermocouple exposed to 5cc 4°C rapid cold saline infusion can discriminate "Good", "Fair", and "Poor" PV occlusions. The lowest temperature drop post cold saline injection and the rate of rewarming recorded from the distal ring thermocouple allow high degree of

discrimination and confidence regarding the occlusion quality. Quality occlusions correlate strongly with PV isolation success. In this study, “Good” rated occlusions resulted in 100% and 97% success rate for PVI with and without dye, respectively. “Fair” rated occlusions resulted in 82% and 91% success rate for PVI with and without dye, respectively and only 10% PVI was documented with “poor” occlusions. This is the first investigations of this simple concept and will lead to a significant reduction for the need for dye and fluoroscopy. This assessment of pre-ablation occlusion positively correlates to ablative success reducing the dependency on post ablation indicators such as thaw times. This will also allow for greater confidence when aiming for single cryo-application in each vein. Furthermore, the potential for the technology to be adapted to quantitate the efficacy of the occlusion through the Cryoconsole system is clear. This could make the CryoConsole capable of alerting the operator whether the PV occlusion is “Good”, “Fair”, or “Poor” and whether cryo-application should be initiated.

References

1. Neumann T, Vogt J, Schumacher B, et al. Circumferential Pulmonary Vein Isolation with the Cryoballoon Technique. J. Am. Coll. Cardiol. 2008;52:273-278.
2. Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, Jordaens L. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. Eur. Heart J. 2007;28:2231-2237.
3. Su W, Kowal R, Kowalski M, Metzner A, Svinarich JT, Wheelan K, Wang P. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. Heart Rhythm 2015;12:1658-1666.

4. Siklódy C, Minners J, Allgeier M, Allgeier H-J, Jander N, Keyl C, Weber R, Schiebeling-Römer J, Kalusche D, Arentz T. Pressure-guided Cryoballoon Isolation of the Pulmonary Veins for the Treatment of Paroxysmal Atrial Fibrillation. J. Cardiovasc. Electrophysiol. 2010;21:120–125.
5. Ciconte, G, Mugnai G, Sieira J, V et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections following second-generation cryoballoon ablation. Circ. Arrhythm. Electrophysiol. 2015;8:1359-1365
6. Aryana A, Mugnai G, Singh SM, Pujara DK, Asmundis Cde, Singh SK, Bowers MR, Brugada P, d'Avila A, O'Neill PG, Chierchia G-B. Procedural and biophysical indicators of durable pulmonary vein isolation during cryoballoon ablation of atrial fibrillation. Heart Rhythm (2016);13:424-432.

Figure Legends

Figure 1: A 28mm Cryoballoon Arctic Front Advance equipped with a conductive distal ring attached to a thermocouple.

Figure 2: Distinct temperature profiles described for the three occlusion levels post injection of 5cc 4°C 50% dye/saline (left panel) and 4°C cold saline only (right panel). After reaching the lowest temperature post injection the average rate of recovery during "Good", "Fair", and "Poor" occlusions is tracked for 10 seconds.

Figure 3: The rate of temperature recovery during the 10 seconds post cold saline injection. “Good” occlusion is defined by the slowest recovery, the fastest recovery defines the “Poor” occlusion, and intermediate recovery defines the fair occlusion.

Figure 4: The internal balloon temperature as recorded by the console at different stages of the cryo-ablation and thaw with “Good”, “Fair”, and “Poor” PV occlusion. The mean and standard deviation temperature data after 30 and 60 sec. and the lowest temperature achieved during the freeze cycle is shown on panel A. The thaw time from the nadir temperature to 0 and 15°C and balloon deflation is shown in panel B.

Figure 5: An example of the differences in gross pathology, ring electrode thermocouple temperature and inner balloon/console temperature post cold saline injection during “Poor” and “Good” occlusion (in the same animal). A lesion resulting from a poor injection is shown in panel A. The PV tetrazolium stained tissue and the trichrome stain histology demonstrate a partially ablated orifice and a large gap of surviving tissues due to the partial occlusion. In contrast a “Good” occlusion resulted in circumferential lesion with no surviving PV sleeve myocardium in Panel B. The minimal temperature drop and rapid recovery demonstrating “Poor” occlusion versus the marked temperature drop and slow recovery with the “Good” occlusion is shown in Panel C. The internal balloon temperature and console thaw times corroborate the pre-ablation “Good” and “Poor” occlusions (panel D and E, respectively).

Table 1 : Occlusion Parameters

Saline Injection Parameters	"Good" Dye	"Good" No Dye	"Fair" Dye	"Fair" No Dye	"Poor" Dye	"Poor" No Dye
Dye Dissipation Duration	67 ± 45	N/A	19 ± 8	N/A	6 ± 3	N/A
No. of test occlusions	N=33	N=74	N=46	N=22	N=34	N=30
Baseline ˚C	37.3±1.2 †^{NS} ‡^{NS} §^{NS}	37.7±1.4 ‡^{NS} §^{NS}	37.7±1.0 †^{NS} ¶^{NS}	37.3±1.7 ¶^{NS}	37.8±0.7 †^{NS}	37.5±1.5
Min ˚C	31.0±4.2 †^{NS} ‡^{NS} §$^{\#}$	29.9±4.2 ‡^{NS} §***	32.7±4.0 †^{NS} ¶$^{\#}$	31.5±4.9 ¶$^{\#}$	35.4±2.0 †$^{\#}$	34.1±2.6
Δ ˚C	6.2±4.2 †$^{\#}$ ‡$^{\#}$ §*	7.7±4.4 ‡$^{\#}$ §***	5.1±3.7 †^{NS} ¶*	5.8±5.0 ¶$^{\#}$	2.4±2.0 †$^{\#}$	3.4±2.3
% Return at 5 sec	18±14 †^{NS} ‡** §***	15±12 ‡* §***	36±23 †^{NS} ¶*	31±23 ¶$^{\#}$	50±33 †^{NS}	45±30
Internal Temp @ 60 sec	-55 ± 9 †^{NS} ‡$^{\#}$ §*	-55 ± 9 ‡$^{\#}$ §***	-49 ± 9 †^{NS} ¶***	-51 ± 10 ¶***	-37 ± 3 †^{NS}	-40 ± 6
Internal Temp Nadir	-62 ± 8 †^{NS} ‡* §***	-60 ± 9 ‡$^{\#}$ §**	-51 ± 5 †^{NS} ¶**	-55 ± 11 ¶**	-41 ± 6 †^{NS}	-44 ± 6
Thaw Time to 0˚C	11.5 ± 4.8 †^{NS} ‡$^{\#}$ §***	11.9 ± 4.8 ‡^{NS} §***	8.5 ± 2.1 †$^{\#}$ ¶*	10.5 ± 5.2 ¶***	4.3 ± 1.3 †$^{\#}$	6.0 ± 2.8
Success Rate % (No. of PVI/No. of PVs)	100% (17/17)	97% (38/39)	82% (9/11)	91% (10/11)	0% (0/23)	10% (3/30)

†= Dye vs None at Same Occlusion Rating, ‡ = Good vs. Fair, § = Good vs. Poor, ¶ = Fair vs Poor
*****= p≤0.0001, ** = p≤0.001, * = p≤0.01, # = p≤0.05, NS = not significant**

FIGURE 1: Cryoballoon

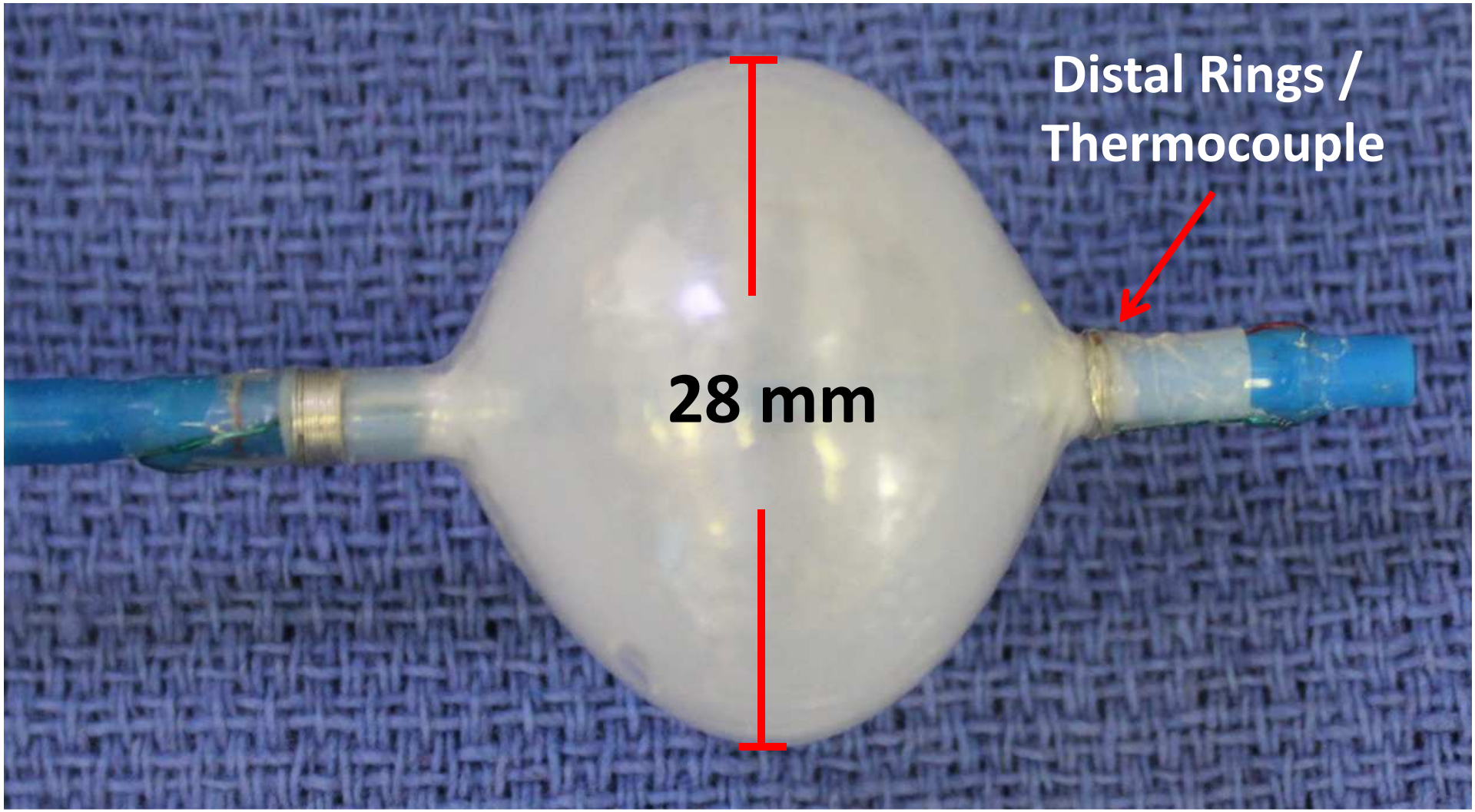
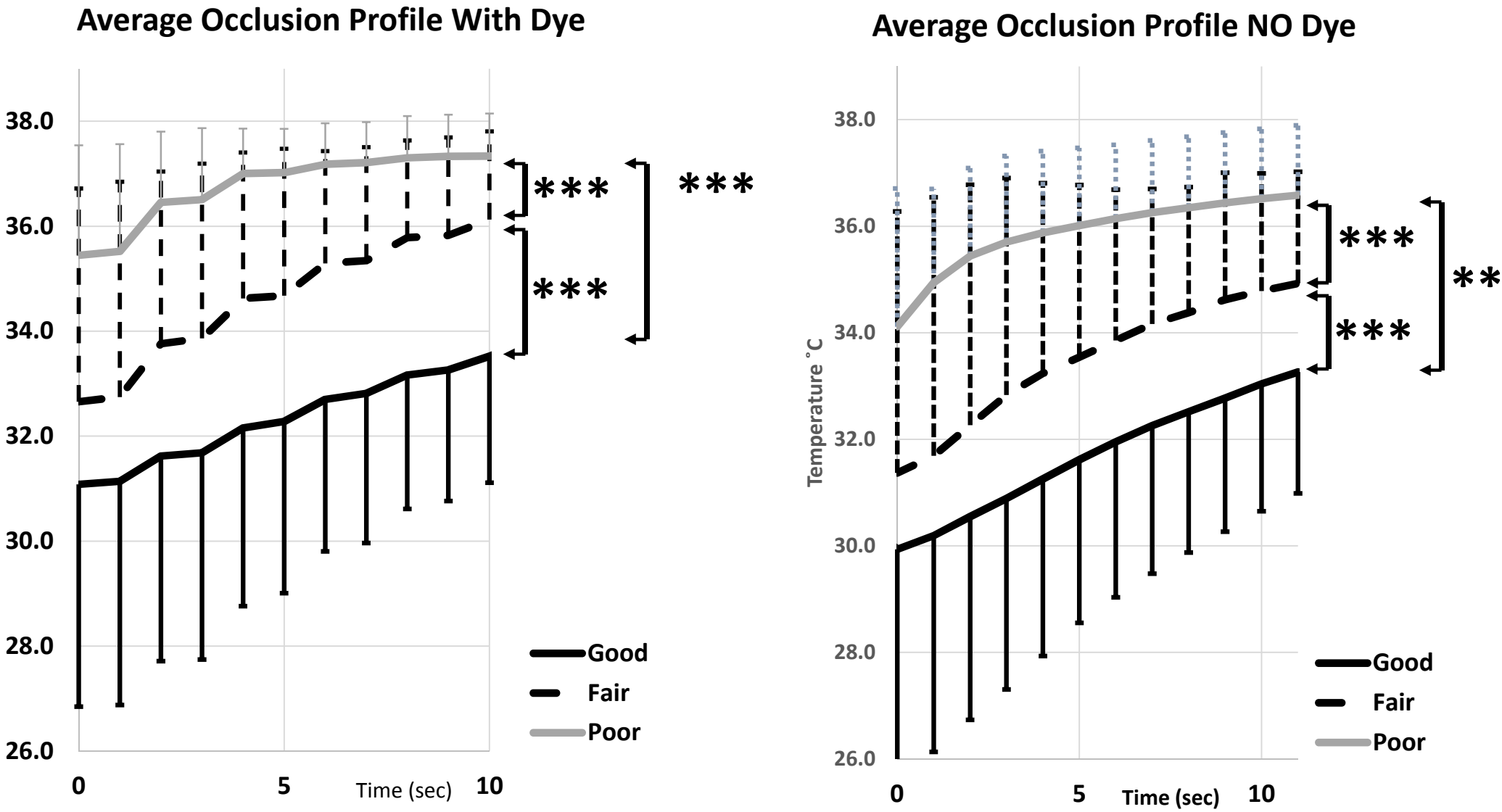


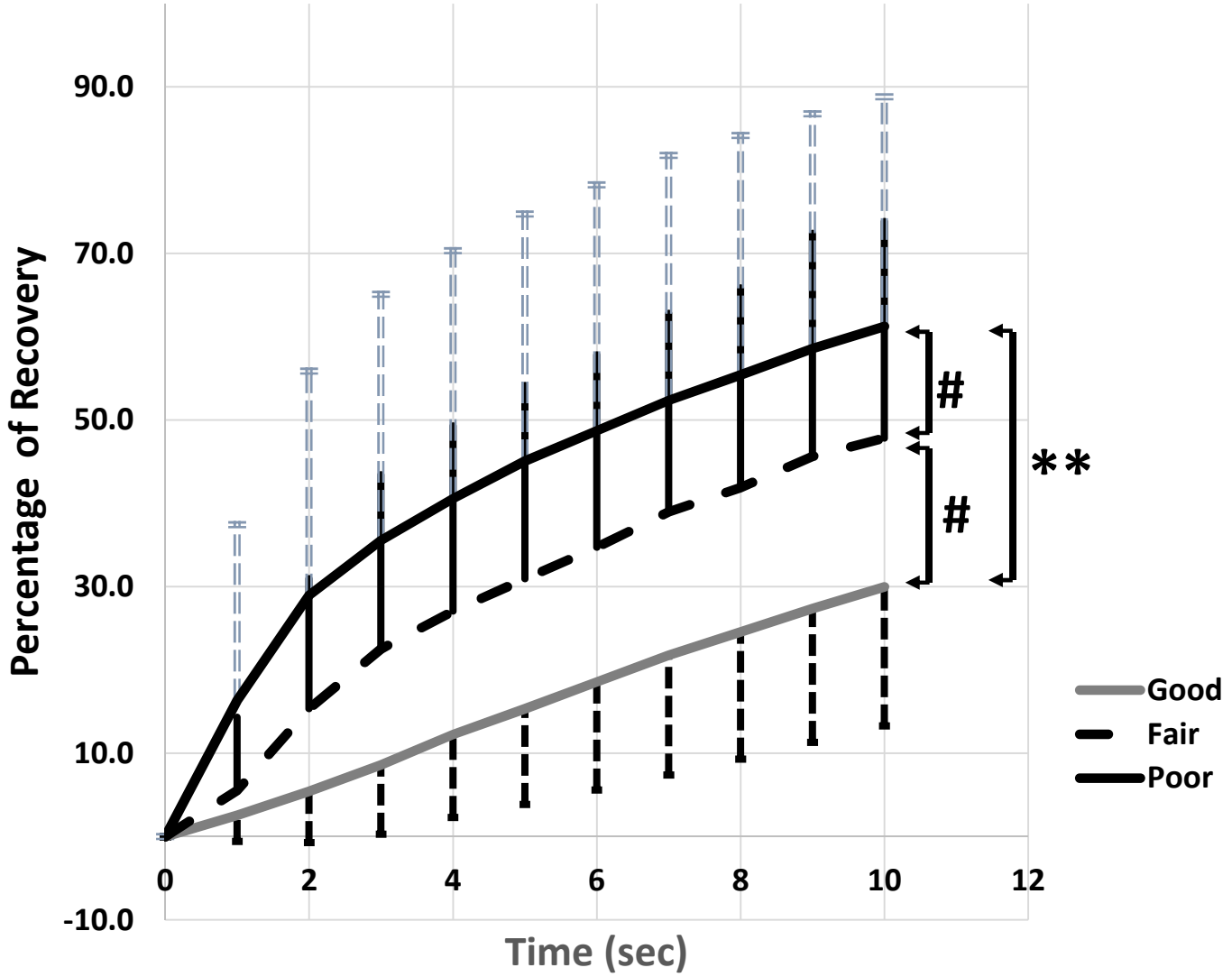
FIGURE 2: Occlusion Profile Post Cold Saline Injection



***= p≤0.0001, ** = p≤0.001, * = p≤0.01, # = p≤0.05, NS = Not significant

Dye N number; Good=33, Fair=46, Poor=34 : No Dye N number; Good=74, Fair=22, Poor=30

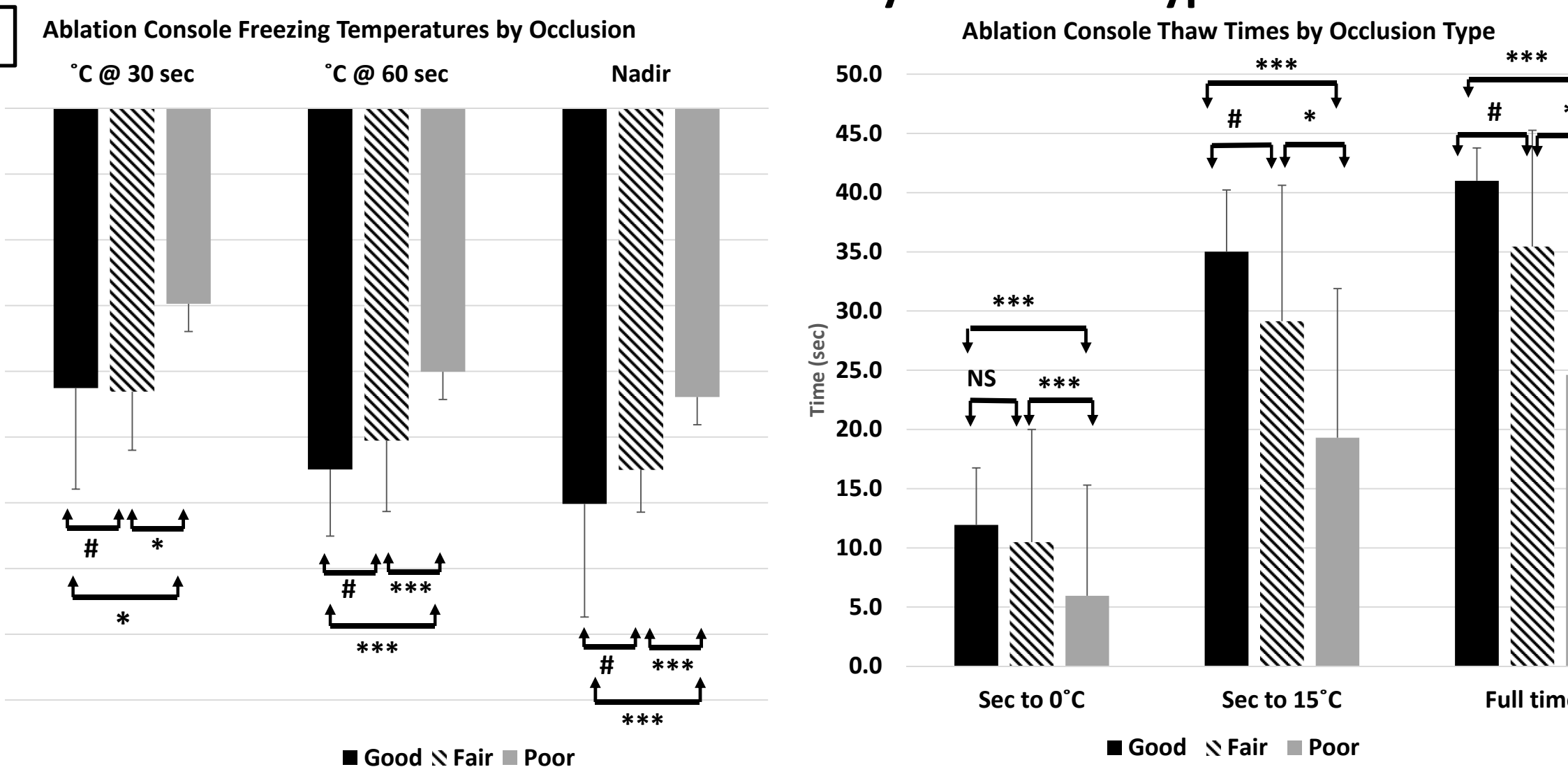
FIGURE 3: Percent rewarming rate after cold saline injection



***= p≤0.0001, ** = p≤0.001, * = p≤0.01, # = p≤0.05, NS = not significant

Dye N number; Good=33, Fair=46, Poor=34 : No Dye N number; Good=74, Fair=22, Poor=30

FIGURE 4: Console Data by Occlusion Type



***= p≤0.0001, ** = p≤0.001, * = p≤0.01, # = p≤0.05, NS = not significant

Dye N number; Good=33, Fair=46, Poor=34 : No Dye N number; Good=74, Fair=22, Poor=30

FIGURE 5: An example of Poor vs. Good occlusion