

Termination of Atrial Fibrillation With Epicardial Cooling in the Oblique Sinus



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ABSTRACT

OBJECTIVES This study aimed to determine if epicardial cooling could repeatedly terminate induced atrial fibrillation (AF) in a canine heart.

BACKGROUND Rapid termination of AF could control symptoms and prevent atrial remodeling; however, defibrillation by internal electrical cardioversion is not tolerable to most patients. Cooling of the epicardium slows atrial conduction and may provide a less painful method to quickly terminate AF.

METHODS AF was induced with atrial myocardial epinephrine injections and rapid atrial pacing in an open-chest canine. Attempts at termination were performed with a small metal device that was either cooled to 5°C or kept at body temperature (control module). The device was placed on the epicardial surface in the oblique sinus. The time from device contact to termination of AF was recorded.

RESULTS In 5 different canine studies, there were 57 attempts at AF termination with either a 5°C module (34 attempts) or a control module (23 attempts). The median (interquartile range [IQR]) time to AF termination was 24 s (IQR: 15 to 35 s) for the 5°C therapy and 100 s (IQR: 47 to 240 s) for the body temperature treatments ($p < 0.001$). In the control group, there were 8 AF episodes that continued up to 4 min. Subsequent application of the 5°C cooling module terminated AF in all cases.

CONCLUSIONS Epicardial cooling in the oblique sinus is effective for repeated termination of AF in a canine heart. If reproduced in human studies, epicardial cooling with an implantable device may provide a method for management of patients with AF. (J Am Coll Cardiol EP 2018;4:1362-8) © 2018 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) afflicts >5 million Americans and millions more around the world (1). By 2030, >12 million Americans will be affected (2). For many, it is a major detriment to their quality of life. Unfortunately, current medical and procedural therapies are only modestly effective. Pharmacological efforts have been disappointing, with no

benefit with regard to mortality, prevention of stroke, quality of life, or reduction in health care use (3). Non-pharmacological strategies, in particular, catheter ablation, have shown promise for paroxysmal AF, although definitive studies are ongoing (CABANA [Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial]; NCT00911508) (4).

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Although ablation may be moderately effective in paroxysmal AF, the effectiveness is quite limited for the persistent form and worsens with increasing age and comorbidities (4). Because of these limitations, a device-based strategy that painlessly and promptly terminates AF after an episode begins would be a significant advance.

Atrial defibrillation with low-energy synchronized shocks by an implanted device has been proven to be effective for some patients, but is not tolerated by many due to discomfort (5-8). As an alternative to electrical shocks, myocardial cooling slows cardiac electrical conduction because of the sensitivity of ion channels to low temperature and may provide a method for defibrillation (9-14). Furthermore, brief mild epicardial cooling is unlikely to cause significant pain.

In a previous study, we demonstrated that external myocardial cooling consistently slowed atrial conduction in the canine heart and terminated simulated AF (15). Cold therapy was delivered with a device that used the Peltier effect, in which electrification of dissimilar conductors (p-doped and n-doped silicon) generate a thermal gradient. This type of device could be made compatible with current implantable defibrillator pulse generators, and thus represents a permanent implantable cooling method. In combination with an electrocardiographic monitoring system, cold temperature treatment could be applied shortly after AF onset to terminate the arrhythmia before a prolonged episode could manifest. It could be delivered repeatedly, and thus potentially prevent the adverse atrial remodeling associated with long episodes of AF, halting disease progression (16).

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Our previous study demonstrated that cooling slows and halts conduction. However, whether a strategically placed cooling element can consistently terminate AF is unknown. Therefore, we performed a prospective canine study to test the hypothesis that external myocardial cooling in the oblique sinus can reliably terminate AF.

METHODS

ANIMAL PREPARATION. Six mongrel canines, mean weight of 26 kg, underwent acute open-chest procedures. One study was excluded from analysis as discussed in the following. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals issued by the National Institutes of Health following Institutional Animal Care and Use Committee approval.

Animals were fasted overnight (for 12 h) before the procedure. Sedation was provided with intravenous diazepam (5 mg) and ketamine (10 mg) for induction. After intubation, 1% to 3% inhaled isoflurane was administered to maintain anesthesia.

After skin preparation, electrocardiographic (ECG) leads were placed in standard locations. Vascular access was obtained using the modified Seldinger method. A decapolar catheter was placed in the coronary sinus via an 8-F right external jugular sheath, and a multipolar catheter was advanced to the high right atrium via an 8-F femoral sheath. Blood pressure was continuously monitored via a 7-F femoral sheath. Catheters and surface leads were connected to the LabSystem Pro EP recording system (BARD Electrophysiology, Lowell, Massachusetts) to monitor intracardiac and ECG tracings throughout the procedure.

With the dog in a supine position, a midline incision was made over the length of the sternum, which was then divided with a bone saw to allow access to the heart. The pericardium was opened, and the oblique sinus was visualized.

ARRHYTHMIA INDUCTION AND THERAPY ASSESSMENT. AF was induced with a combination of epinephrine injection in the free wall of the left and right atrial appendages, followed by rapid atrial pacing using a Bloom stimulator (Fischer Medical, Wheat Ridge, Colorado). To maintain a stable, consistent electrophysiological milieu, 0.1 mg of epinephrine was injected into each appendage before each attempt at AF induction, regardless of the rhythm at the time. Rapid atrial pacing through the high right atrial catheter was then delivered. Atrial pacing was stopped when the atrial electrogram showed the variable morphology and cycle length consistent with AF. Sustained AF was required for 30 s before any intervention. This also allowed time for the atrial myocardial temperature to return to baseline between treatments.

After each successful induction of AF, the animal was treated with either a cooling (5°C) or control (body temperature) treatment. In experiment 1, the primary objective was determination of adequate function of the experimental setup; thus, there were primarily cooling attempts with only 1 control attempt. Experiment 2 followed a computer randomized pattern of treatments. All subsequent experiments alternated each treatment between the cooling device and the control module to ensure a near equal number of each treatment.

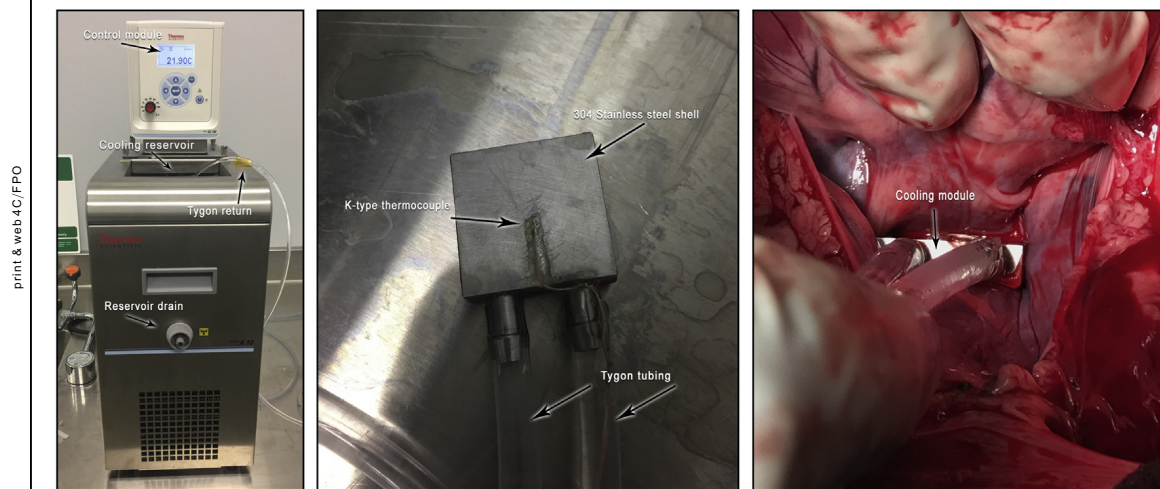
The experimental cooling module was maintained at the chosen temperature, then placed in the oblique sinus after 30 s of AF (Figure 1). If AF persisted for 4 min, the opposite therapy (cold or control module)

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ECG = electrocardiographic

IQR = interquartile range

FIGURE 1 Photographs of the SC100-10A Lab Recirculator

(Left to right) Photographs of the SC100-10A lab recirculator (Thermo Fisher Scientific, Waltham, Massachusetts), the cooling module, and the cooling module in position in the oblique sinus.

was applied during ongoing arrhythmia. Following completion of the procedure, the animals were sacrificed by induction of ventricular fibrillation.

PRIMARY STUDY OUTCOME. The primary outcome was the termination of AF following delivery of a cold temperature treatment to the myocardium in the oblique sinus compared with placebo (body temperature device).

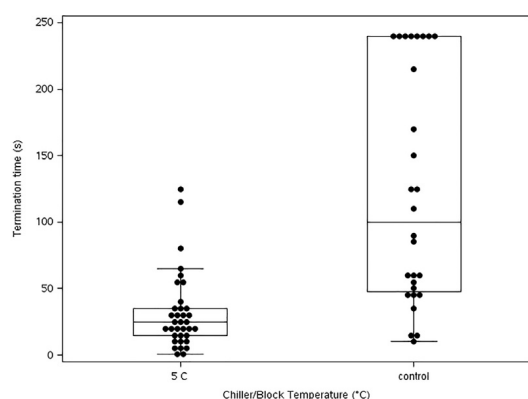
EXPERIMENTAL COOLING MODULE. A small electric device using the Peltier effect, as used in our previous experiments, will be essential for the eventual clinical device. However, in these studies, we opted to use a simpler, quickly adjustable device to focus on the effectiveness of myocardial cooling rather than concurrently evaluate device function. The experimental cooling module used in these studies was a fluid heat exchanger that circulated chilled deionized saline through a thin, highly conductive, metal shell, with an interior designed to carefully channel fluid flow to optimize heat transfer. The cooling module simulated the size and constant temperature expected from a thermoelectric Peltier device. A SC100-10A lab recirculator (Thermo Fisher Scientific, Waltham, Massachusetts) recirculated constant temperature 5°C deionized water at 0.83 l/min through a plastic tubing circuit. The surface temperature at the cooling device at the interface with the atrial epicardium was recorded by a 12-channel thermocouple datalogger TM500 (Extech Instruments, Waltham, Massachusetts). For control therapies, a second

device was kept inside the canine thorax to maintain body temperature until moving it to the oblique sinus for a treatment attempt.

LOCATION OF DEVICE PLACEMENT. The epicardium in the oblique sinus is an accessible and stable location for an epicardially-placed device, but was chosen as the treatment location for several other reasons. This region encompasses a large mass of atrial myocardial and/or pulmonary venous tissue that is important for the electrical function of the left atrium, but it has a lesser contribution to the mechanical efficiency. The posterior left atrium is also important in the activity of the intrinsic autonomic nervous system because it is the location of many sites with high ganglionated plexus density (17). These sites may have a major contribution to the initiation and sustenance of AF (18,19). Lastly, our previous attempts at atrial cooling suggested that this site may be the best option for termination of AF (15).

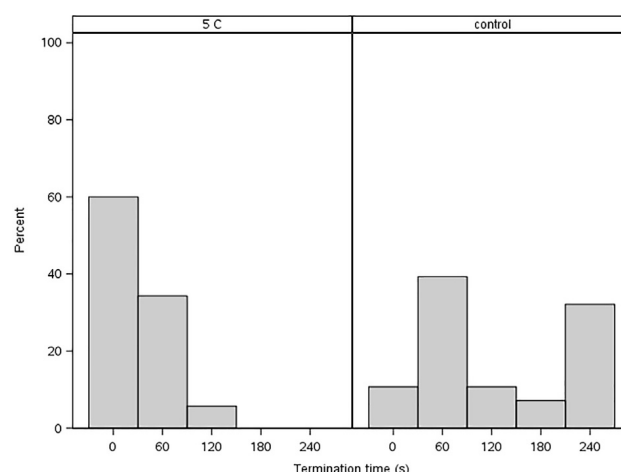
STATISTICAL ANALYSIS. Continuous variables are presented as a mean $\pm$ SD or median (quartile), as appropriate. Differences in time to termination of AF between the control and cooling therapy was tested using a nonparametric Wilcoxon rank sum test. For trials that failed to terminate within 4 min, 240 s to termination was used. A secondary sensitivity analysis with exclusion of these trials was also evaluated, and the results were similar. To account for repeated experiments within animals, a mixed linear regression model was fit with a random intercept for

FIGURE 2 Comparison of the Time From Module Contact to Termination of Atrial Fibrillation



Comparison of the time from module contact to termination of atrial fibrillation between the 5°C module and the body temperature module. Eight attempts that did not terminate atrial fibrillation by 240 s are included at a time of 240 s in the control group.

FIGURE 3 Time From Module Contact to Termination of Atrial Fibrillation



Bar histogram of time from module contact to termination of atrial fibrillation in canines treated with the 5°C module and the body temperature module.

animals. Within this model framework, differences in time to termination for the cooling module versus the control module were tested, and the beta estimate with 95% confidence interval was summarized. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for analyses, and 2-tailed p values ≤ 0.05 were considered statistically significant.

RESULTS

The results from 1 experiment were discarded due to equipment malfunction. In the remaining 5 studies, there were 57 attempts at AF termination with either a 5°C module (34 attempts) or a control, body temperature module (23 attempts). The cooling device maintained a steady-state, module–atrial surface interface temperature of $14.29 \pm 0.69^\circ\text{C}$, with a mean time to steady state of 14.00 ± 3.25 s. There were no acute complications during any of the studies, including no obvious gross injury from the cooling device.

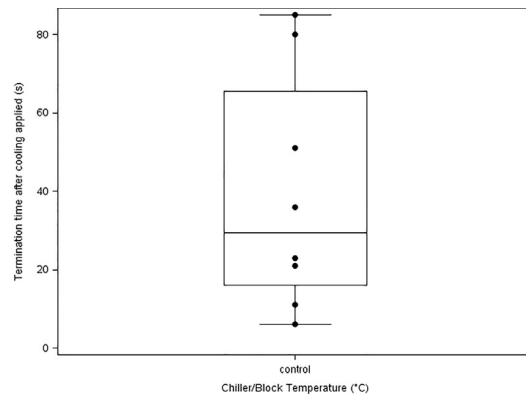
The median (interquartile range [IQR]) time to AF termination was 24 s (IQR: 15 to 35 s) for the 5°C therapy and 100 s (IQR: 47 to 240 s) for the body temperature treatments ($p < 0.001$) (Figure 2). Application of the 5°C device terminated AF in 85.7% of attempts in <60 s, compared with 44.8% of attempts within the same time period for the body temperature device ($p < 0.001$). AF was sustained past 120 s in a single attempt (2.9%) with 5°C therapy, whereas AF continued past 120 s in 44.8% of control

trials ($p < 0.001$) (Figure 3). In the control group, there were 8 AF episodes that continued up to 4 min. At that point, the 5°C cooling module was applied, and it terminated AF in all cases, with a median time of 30 s (IQR: 16 to 66 s) (Figure 4). There were no episodes of AF treated with the 5°C therapy that lasted up to 4 min.

There was significant variability in the treatments on time to termination of AF among the animals, which seemed to be driven by differences in the control attempts (Figure 5). Results of mixed linear regression showed strong differences between treatments while controlling for the animal effects ($p < 0.001$; beta estimate for cooling: -90 ; 95% confidence interval: -60 to -118).

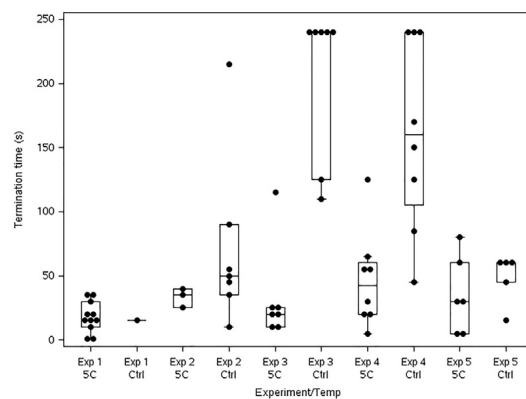
DISCUSSION

We found that the application of a cooling module to chill the dome of the left atrium via the oblique sinus successfully terminated all episodes of AF, which supported the concept that delivery of hypothermia by an implanted device might be a viable option for AF management. In young, healthy canines, spontaneous termination of AF was expected to occur. Therefore, the time to termination following application of a 5°C cooling module was compared with the time following placement of a body temperature control device, accounting for potential effects of mechanical pressure and interference in the oblique sinus. Compared with the control group, the 5°C

FIGURE 4 Time From 5°C Module Contact to Termination of Atrial Fibrillation

Time from 5°C module contact to termination of atrial fibrillation in episodes when atrial fibrillation did not terminate by 240 s with the body temperature module.

cooling module reduced the median time to termination of AF by 76 s (Figure 2), which was strongly significant. Moreover, 8 AF episodes lasted 4 min following control device placement compared with no such episodes following cooling. In these cases, application of cold after failure of 4 min of the control module terminated the resistant episode in a median of 30 s (Figure 4), further demonstrating the physiological effect of atrial cooling in the oblique sinus.

FIGURE 5 Time From Contact of Module to Termination of Atrial Fibrillation for Each Experiment

Time from contact of module to termination of atrial fibrillation for each experiment (Exp) separated by type of treatment. Eight attempts that did not terminate atrial fibrillation by 240 s are included at a time of 240 s in the control (Ctrl) groups. Exp 1 only contained 1 Ctrl treatment, as explained in the text.

Importantly, during the cooling treatment, temperatures never fell to $<5^{\circ}\text{C}$, which avoided freezing and tissue injury.

The use of cold has been well established in the treatment of arrhythmias, with a history spanning decades. Cryotherapy has been used as a valuable surgical ablation tool from early epicardial accessory pathway elimination to modern surgical AF treatment (20,21). Catheter-based cryoablation has likewise been used as a now common method for AF ablation and for some ventricular arrhythmias (22-24). There have also been previous examples of cold being used to terminate arrhythmias without causing damage to cardiac tissue, such as the termination of ventricular tachycardia with cold saline injection (14). This extensive history of the safe use of cryotherapy for the effective treatment of arrhythmias further supports the rationale for the development of this approach.

Several mechanisms may account for the ability of cold temperatures to terminate AF. The myocyte membrane channels responsible for ionic current flow are temperature sensitive, so that conduction velocity is reduced during hypothermia (9-11). The cooling module was positioned over the dome of the left atrium, so that a sufficiently large area of atrial myocardium might have been excluded from reentry to terminate the arrhythmia. The oblique sinus also subtends the pulmonary vein ostia posteriorly, which is a common source of AF triggers (25); cold may have suppressed discharging triggers. This anatomic region also contains a high density of cardiac autonomic ganglionated plexus sites, which have been linked to the initiation and persistence of AF (18,19). However, these potential mechanisms are entirely speculative and the way in which cooling terminates AF may be unrelated to some or all of these. Further experiments would need to be designed to assess the precise mechanism of termination.

In our experiments, we used a fluid-based heat exchange module that mimicked the size and function of a solid-state Peltier element. The cooling module maintained 5°C because this temperature would be attainable with an implanted electrical device using the Peltier effect. Furthermore, this temperature was much warmer than temperatures that cause freezing and injury of cardiac tissue (26). The cooling module was used as an experimental and budgetary expedient. In a previous study, we demonstrated cooling with a Peltier device that used the thermoelectric effect to apply hypothermia. Such devices deliver an electric charge to the interface between bonded p-doped and n-doped semiconductors to generate a thermal gradient. Because they are electrically driven, they can leverage existing

implantable defibrillator technology to be powered by currently available pulse generators. This would enable rapid clinical development.

Following permanent placement in the oblique sinus through a minimally invasive approach ([Online Figure 1](#)), Peltier coolers could repeatedly deliver cold therapy shortly after AF onset, thus preventing adverse atrial remodeling. AF detection could occur through electrodes on the device or could use the monitoring functions of a coupled pacemaker system, if there is a pre-existing system or one is otherwise needed. This study provided evidence that such a system might be a clinically effective management option for AF. Initially, this would likely be added for patients with paroxysmal AF who are not responding to medications or ablation. However, if the treatment effect is noted to be robust and repeatable, this might ultimately be used as first-line therapy in paroxysmal, or even persistent, AF.

Although there has been great clinical enthusiasm for catheter ablation to treat AF, the recurrence rates have been disappointing, effectiveness is limited in persistent forms, and published ablation reports have included predominantly younger patients with AF ([4](#)). There is a pressing need for the development of an effective therapeutic option for AF, the most costly and commonly encountered arrhythmia in clinical practice ([2,4,27](#)). Implantable atrial defibrillators were developed in the mid-1990s and were found to be effective with success rates of 82% for acute termination of AF ([5](#)). However, device use was abandoned due to shock-related pain.

We developed a novel device-based strategy using a potentially painless hypothermic method that might enable termination of clinical AF. In previous experiments in acute canine models, we consistently achieved clinically significant transmural cooling of the atria to the target temperature using modified Peltier elements ([15](#)). Furthermore, we found cooling using the prototype transiently slowed atrial conduction, created conduction block, and terminated pacing-mimicked AF ([15](#)). In this study, we demonstrated that cold therapy at similar temperatures and with a similar device could consistently terminate sustained AF ([Figure 2](#)).

STUDY LIMITATIONS. The primary limitations were related to the use of an animal model. As with any animal study, the ability to translate the results to humans is uncertain. Although the canine model was chosen due to its similarities with human cardiac anatomy and physiology, there are many differences between the 2 species. In this study in particular, the similarity of the AF model to clinical AF in humans was uncertain. Although AF, as defined from an ECG

standpoint, was clearly induced repeatedly, other aspects of the syndrome were not replicated fully. Nevertheless, we believe that the methods used in this study provided the best attempt at replicating human AF to determine efficacy and safety before the inevitable necessity of human studies. We would not anticipate that the clinical device would be used to treat long-standing episodes of AF, but rather quickly terminate episodes shortly after detection. Nevertheless, further studies assessing efficacy in more long-standing episodes of AF might provide increased similarity to the clinical AF seen in patients. Furthermore, the sample size in this study was quite small. Statistical analyses were provided to help summarize data, but should not be over interpreted. Future experiments in canines and then humans will be important to confirm these results.

Cold therapy did not have the same magnitude of effect in each experiment. There was significant variability in the duration of AF and the effects of cooling among animals. This might reflect interindividual variations in cardiac anatomy, changes in autonomic tone, or in device placement. Notably, however, much of the variability in the treatment effect was related to the times to termination in the control attempts. In the young, healthy canines, spontaneous termination of AF was expected; hence, the need for a control group. As might be anticipated, the times to termination with the control treatment varied widely. In contrast, the times to termination in the treatment group were fairly similar for each canine. The fact that the duration of AF following cold therapy was more homogenous than that with the control module might actually be supportive of the effect of cooling across different individuals, but further study would be needed to assess variability in response.

CONCLUSIONS

AF can be terminated with epicardial cooling safely in an acute AF canine model. A cooling module maintained at 5°C placed on the posterior left atrium terminated AF significantly faster than a control body temperature device. Future studies will be needed to assess long-term safety and to determine if these findings can be translated to clinical AF in patients. If so, a cooling device coupled with an ECG monitoring system may provide a painless method for repeatable AF termination.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF is a common arrhythmia that affects millions of people worldwide, with a continually increasing prevalence. AF can have a major negative effect on quality of life and is associated with worsening of heart failure and increased mortality. Early effective treatment may prevent symptoms, complications, and a more persistent syndrome. Current medical and invasive therapies have limited efficacy.

TRANSLATIONAL OUTLOOK: This study demonstrated the potential efficacy of a novel treatment for AF. Application of a cooled device to the epicardial surface of the heart was able to terminate episodes of AF in canines. With further confirmation in larger animal and human studies, an implanted cooling device might be used to painlessly and repeatedly terminate AF quickly after onset to prevent symptoms and adverse effects.

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KEY WORDS atrial fibrillation, atrial remodeling, cold therapy, defibrillation, implantable device

APPENDIX For a supplemental figure, please see the online version of this paper.