The Heart Surgery Forum #2005-1011
8 (5), 2005 [Epub August 2005]
doi:10.1532/HSF98.20051011

Online address: http://cardenjennings.metapress.com/link.asp?id=112496

Dose Response Curves for Microwave Ablation in the Cardioplegia-Arrested Porcine Heart

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ABSTRACT

Introduction: Microwave ablation has been used clinically for the surgical treatment of atrial fibrillation, particularly during valve procedures. However, dose- response curves have not been established for this surgical environment. The purpose of this study was to examine dosimetry curves for the Flex 4 and Flex 10 microwave devices in an acute cardioplegia-arrested porcine model.

Methods: Twelve domestic pigs (40-45 kg) were acutely subjected to Flex 4 (n = 6) and Flex 10 (n = 6) ablations. On a cardioplegically arrested heart maintained at 10-15°C, six endocardial atrial and seven epicardial ventricular lesions were created in each animal. Ablations were performed for 15 s, 30 s, 45 s, 60 s, 90 s, 120 s, and 150 s (65 W, 2.45 GHz). The tissue was stained with 2,3,5-triphenyl-tetrazolium chloride and lesions were sectioned at 5 mm intervals. Lesion depth and width were determined from digital photomicrographs of each lesion (resolution ± .03 mm).

Results: Average atrial thickness was 2.88 ± .4 mm (range 1.0 to 8.0 mm). 94% of ablated atrial sections created by the FLEX 4 (n = 16) and the FLEX 10 (n = 16) were transmural at 45 seconds. 100% of atrial sections were transmural at 90 seconds with the FLEX 10 (n = 14) and at 60 seconds with the Flex 4 device (n = 15). Lesion width and depth increased with duration of application.

Conclusion: Both devices were capable of producing transmural lesions on the cardioplegically arrested heart at 65 W. These curves will allow surgeons to ensure transmural ablation by tailoring energy delivery to the specific atrial geometry.

INTRODUCTION

A renewed interest in the surgical treatment of atrial fibrillation has been prompted by the introduction of new ablation technology into the operating room [Cox 1997, 2000]. This has allowed surgeons to replace the complicated incisions of the Cox–Maze procedure with linear lines of ablation. This has simplified the surgical treatment of atrial fibrillation and has made it more accessible to surgeons and more widely applicable to patients.

Microwave energy is one of the energy sources that has been widely used in the surgical treatment of atrial fibrillation [Gillinov 2002, Damiano Jr. 2003, Saltman 2003]. The FLEX 4 and FLEX 10 microwave devices (Guidant, Inc., Santa Clara, CA) have been used around the world to produce linear lines of ablation in the atria [Knaut 1999, 2002, Massen 2002, Venturini 2003]. Microwave energy generates heat within tissue by inducing oscillation of dielectric molecules such as water. The kinetic energy produced in these molecules by the microwave field is imparted to the tissue as heat energy. This form of heat production is known as dielectric heating. The penetration of the lesions produced by microwave is dependent on the power, the duration of application, and the type of microwave antennae [Williams 2002a]. The advantage of microwave over radiofrequency energy is that it produces a deeper lesion with more even penetration of the tissue with less surface heating. Tissue temperature exceeds 50°C but remains below 100°C hence reducing the risk of tissue charring [Williams 2002b]. Ablation devices are used surgically to create lines of conduction block in the atria that either block the trigger foci of the arrhythmia or interrupt the macro-reentrant circuits felt responsible for the maintenance of atrial fibrillation. The only guarantee of bi-directional conduction block in myocardial tissue is a transmural lesion. Thus, the effectiveness of any ablation device is judged by its ability to create transmural lesions in the operating room. The effectiveness of ablation must be balanced by device safety. This means a device must be capable of creating a transmural lesion without tissue perforation, charring, or collateral cardiac or extra-cardiac injury. In order to establish the efficacy and safety of an ablation device, precise dose–response curves need to be established in clinically relevant models. This would allow a surgeon to deliver appropriate and adequate energy based on the specific atrial dimensions in each patient. These curves are presently not available for microwave devices.

In this study, the FLEX 4 and FLEX 10 microwave devices were examined. The Flex 4 device has a 4 cm flexible

Received January 14, 2005; accepted March 30, 2005.

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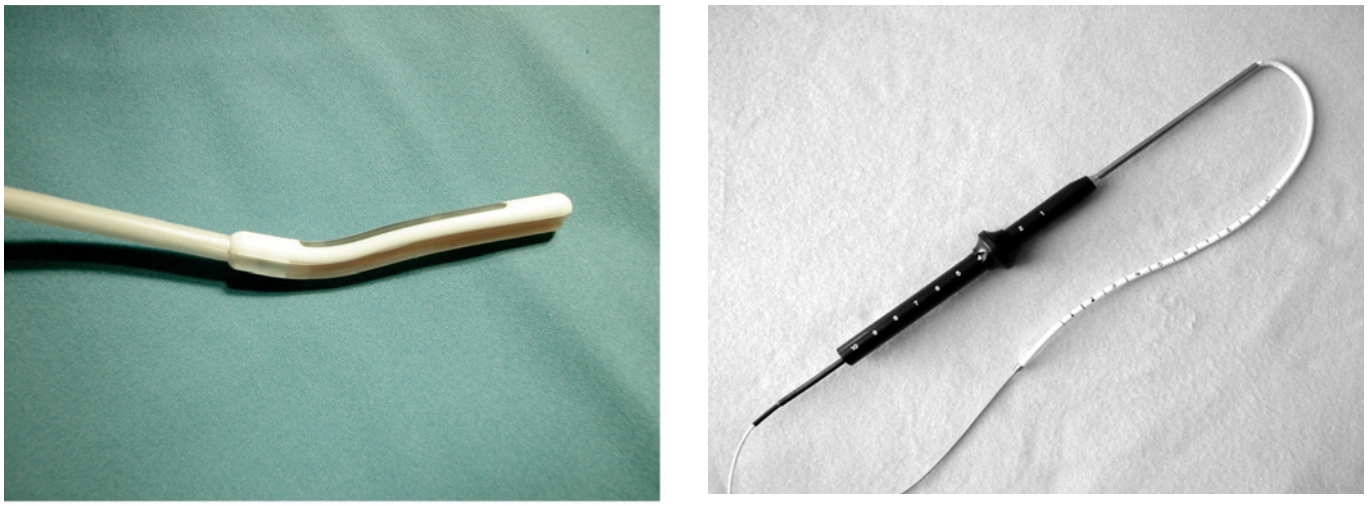

Figure 1. The (a) FLEX 4 and (b) FLEX 10 microwave devices.

antenna with a flexible shaft (Figure 1a). It is capable of producing lesions 4 cm in length. The manufacturers' recommended setting is 65 W for 60 seconds when applied to the endocardial surface of the atria in an arrested heart.

The Flex 10 device consists of an antenna 26 mm long, which is encased in an extremely flexible whip-like Teflon sheath 53.3 cm in length (Figure 1b). The antenna can be adjusted within the sheath to produce ablation lines 2 cm in length per application. The device was introduced mainly for epicardial application on the beating heart. The manufacturers' recommended setting is 65 W for 90 seconds.

In this study, dose–response curves were established for both these devices in a clinically relevant acute porcine model that simulated the most common clinical scenario. Since most patients having atrial fibrillation surgery are undergoing concomitant valve procedures, endocardial and epicardial ablation was examined in the cardioplegically arrested heart.

MATERIAL AND METHODS

Experimental Protocol

Twelve domestic pigs weighing 40-45 kg were used in this study. All animals received humane care in compliance with the 'Guide for the Care and Use of Laboratory Animals' published by the National Institute of Health (NIH Publications 85-23. Revised 1985).

Each animal was pre-medicated, intubated, and anesthetized with 2-4% isoflurane and monitored continuously throughout the procedure. The heart was exposed through a median sternotomy. The superior and the inferior vena cava were circumferentially dissected and isolated with umbilical tapes. A cardioplegic cannula was placed in the proximal aorta. The vena cavae were snared and the aorta was cross-clamped. A cold crystalloid cardioplegic solution (Plegisol(tm), Abbott Laboratories, North Chicago, IL) was introduced into the aortic route at a pressure of 70-80 mm Hg and was given at a calculated volume (10 mL/kg). A myocardial temperature probe was placed into the ventricular septum and normal saline slush was placed topically on the heart. Cardioplegic solution was given at 20-minute intervals to maintain the myocardial temperature between 10-15°C. Right atrial and ventricular lesions were created using the FLEX 4 and FLEX 10 devices. The right atrial lesions were created endocardially at 65 W and durations of 15, 30, 45, 60, 90, and 120 seconds, respectively. Right ventricular ablations were also made epicardially at 65 W and durations of 15, 30, 45, 60, 90, 120, and 150 seconds, respectively. Ablations were performed on 6 animals using the FLEX 4 device and on an additional 6 animals using the FLEX 10 device.

Histological Assessment

At the end of the procedure, 1% 2,3,5-Triphenyl-Tetrazolium Chloride (TTC) was perfused into the aortic root before the removal of the heart. The hearts were removed en bloc and myocardial tissue lesions were examined for evidence of charring and tissue disruption. The hearts were then placed in 1% TTC solution and incubated at room temperature for 45 minutes. Each microwave lesion was sectioned at 4 levels, 5.0 mm apart, and perpendicular to the long axis of the ablation line. Each section was then digitally photographed along with a caliper set at 5 mm, which allowed for calibration. Lesion width, depth, and atrial tissue thickness were analyzed using a computerized software (Adobe Photoshop). The lesion depth and width were measured from the unstained area to the pink halo region surrounding each lesion. The accuracy of this technique was ±0.03 mm. A total of 13 lesions from each animal were examined.

Statistical Analysis

Data were compared with repeated measures analysis of variance with one factor. Data were expressed as mean ± SD and considered significant with $P < .05$.

RESULTS

On gross inspection, the lesions were pale, well demarcated, and clearly visible. The FLEX 4 and FLEX 10 lesions appeared similar. There was a minor amount of tissue shrinkage at higher durations of ablation (90-150 seconds). No tissue disruption was observed. Extensive charring was not seen. The depth of ablation was compared to the atrial wall thick-

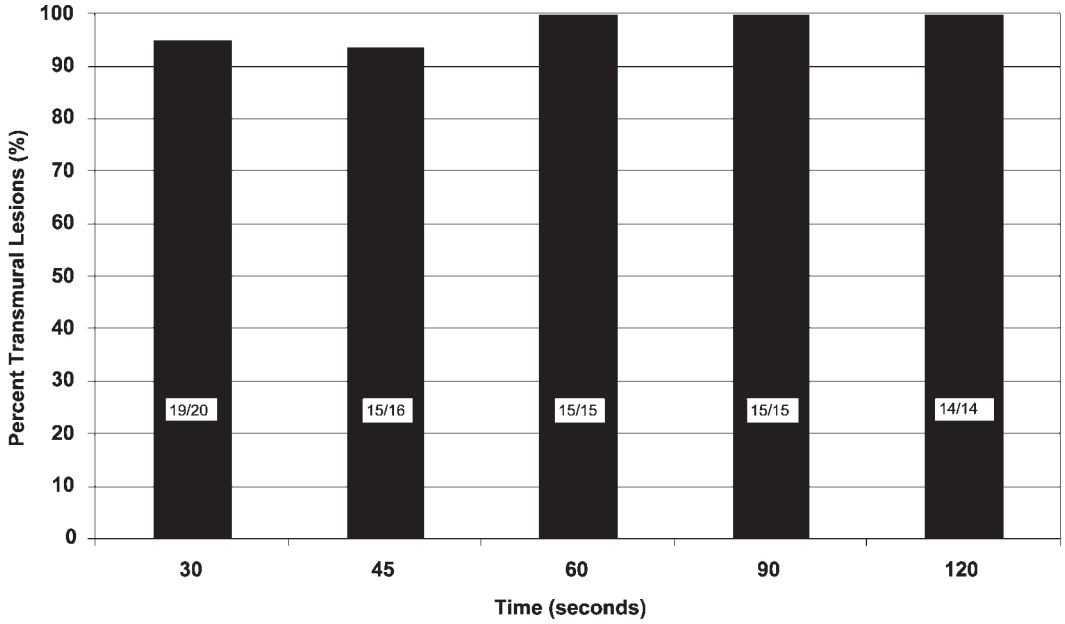

Figure 2. The percentage transmurality versus duration of ablation for the FLEX 4 device.

ness in the region of ablation. The number of transmural sections were then determined. The mean atrial tissue thickness was 2.88 mm with a range of 1.0 mm to 8.0 mm.

Atrial Ablation

Ninety four percent of ablated atrial sections (n = 16) created by the FLEX 4 device were transmural at 45 seconds (65 W) and 100% of atrial sections (n = 44) were transmural at ablation durations 60 seconds and above (Figure 2). Similarly for the FLEX 10 device, 94.0% of ablated atrial sections (n = 16) were transmural at 45 seconds (65 W) and 100% of atrial sections (n = 29) were transmural at greater than or equal to 90 seconds of ablation (Figure 3). The Table summarizes the number of sections that were not transmural, with the corresponding tissue thicknesses.

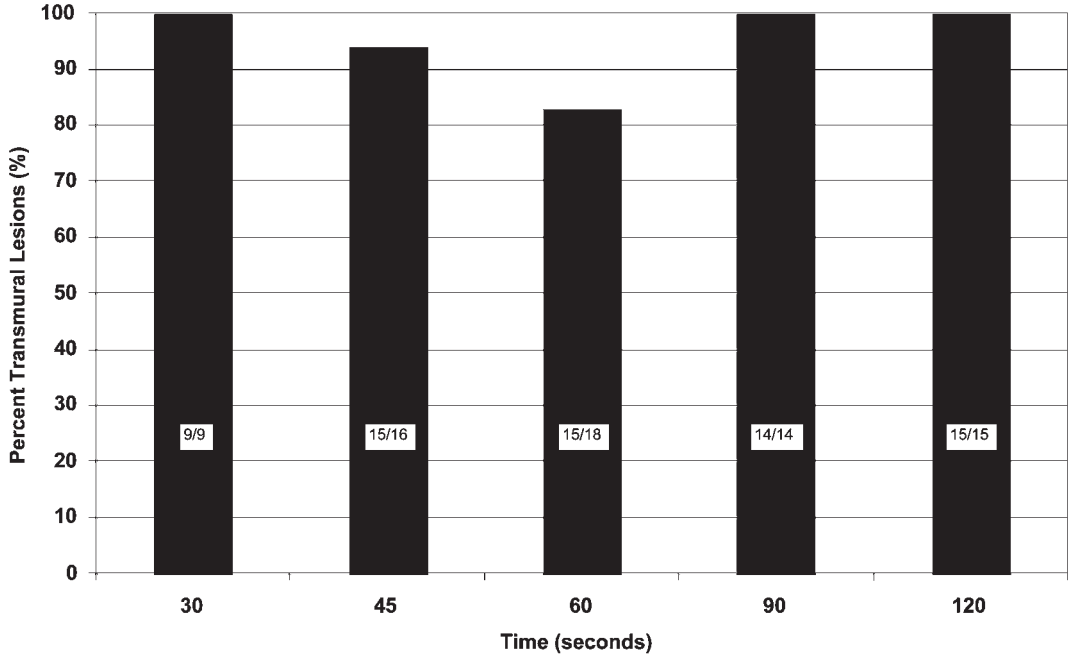

Figure 3. The percentage transmurality versus duration of ablation for the FLEX 10 device.

Number of Nontransmural Sections with Corresponding Tissue Thicknesses

	FLEX 4		FLEX 10	
Ablation time, s	No.	Tissue thickness, mm	No.	Tissue thickness, mm
30	1	3.5	0	N/A
45	1	3.0	3	5.1, 4.9, 6.0
60	0	N/A	1	8.0

Dose–Response Curves

Dose–response curves were established for the FLEX 4 and FLEX 10 devices from right ventricular ablations. The right ventricle was used because the right atrium was too thin to calculate a full dose–response curve. The average right ventricular wall thickness was 8.2 ± 2.9 mm with a range of 3.2 to 17.6 mm. Lesion depth and width increased with duration of ablation for both devices (Figures 4, 5, 6). The lesion depth ranged from 0.5 mm (15 seconds) to 10.6 mm (150 seconds) for the FLEX 4 device and 0.5 mm (45 seconds) to 9.5 mm (150 seconds) for the FLEX 10 device. The mean lesion depth for the FLEX 4 device at 90 seconds (65 W) was 2.4 ± 1.0 mm and the mean lesion depth for the FLEX 10 device at 90 seconds (65 W) was 4.1 ± 1.3 mm ($P < .001$). These data were further analyzed and the maximum lesion depth for the FLEX 4 and FLEX 10 devices was examined. It was noted that the shape of the graphs were similar to that of the mean lesion depth versus time (Figure 5). The maximum lesion depth produced by the FLEX 10 device was consistently deeper than that produced by the FLEX 4 device. The maximum lesion depth produced by the FLEX 4 and FLEX 10 devices after 60 seconds of ablation were 3.5 ± 0.7 mm and 4.8 ± 1.1 mm, respectively ($P < .001$). After 90 seconds of ablation the maximum lesion depth produced by the FLEX 4 and FLEX 10 devices was 3.4 ± 1.3 mm and 5.2 ± 1.2 mm, respectively ($P < .001$).

Lesion widths ranged from 1.5 mm (15 seconds) to 12.3 mm (150 seconds) for the FLEX 4 device and 2.1 mm (45 seconds) to 12.6 mm (150 seconds) for the FLEX 10 device (Figure 6). The lesions created by the FLEX 10 device were significantly deeper and wider than those created by the FLEX 4 device ($P < .001$).

COMMENT

This study demonstrated that the FLEX 4 and FLEX 10 microwave devices were capable of producing transmural atrial lesions on the arrested heart in a surgically relevant model. The lesions were well defined and easily visible. Tissue charring was seen infrequently. For the Flex 4, all lesions were transmural with ablations of 60 seconds or greater. For the Flex 10, it required 90 second ablations to guarantee transmurality. This was partly due to the very thick atrium, as these ablations were carried out over the crista terminalis, and all sections that did not achieve transmural lesions were >4.9 mm in thickness. These data are consistent with the dose–response curves on the thicker ventricular muscle. This strongly suggests that a single fixed ablation time of <90 seconds will not consistently achieve transmural lesions in tissue thickness exceeding 5 mm. Moreover, it points out that ablations need to be tailored to the specific atrial dimensions, which can be thicker under pathologic conditions.

These data were acquired in a model that is similar to the clinical situation. The hearts were arrested with cardioplegia

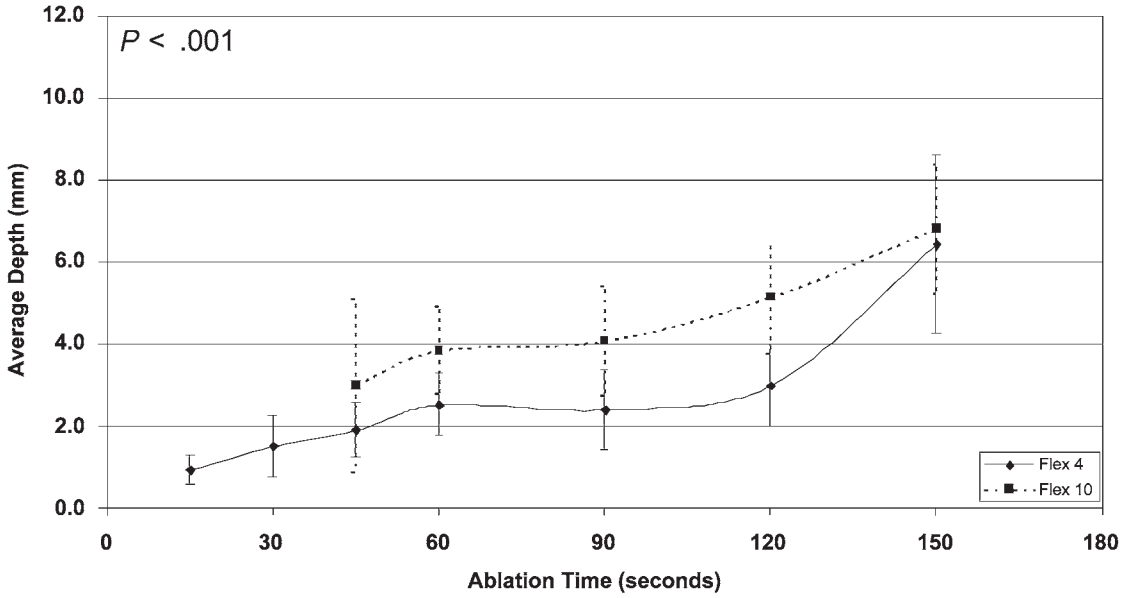

Figure 4. The average lesion depth versus time for the FLEX 4 (solid line) and FLEX 10 (dotted line) devices. Lesion depth was significantly deeper for the FLEX 10 device compared to the FLEX 4 at any given duration of ablation ($P < .001$).

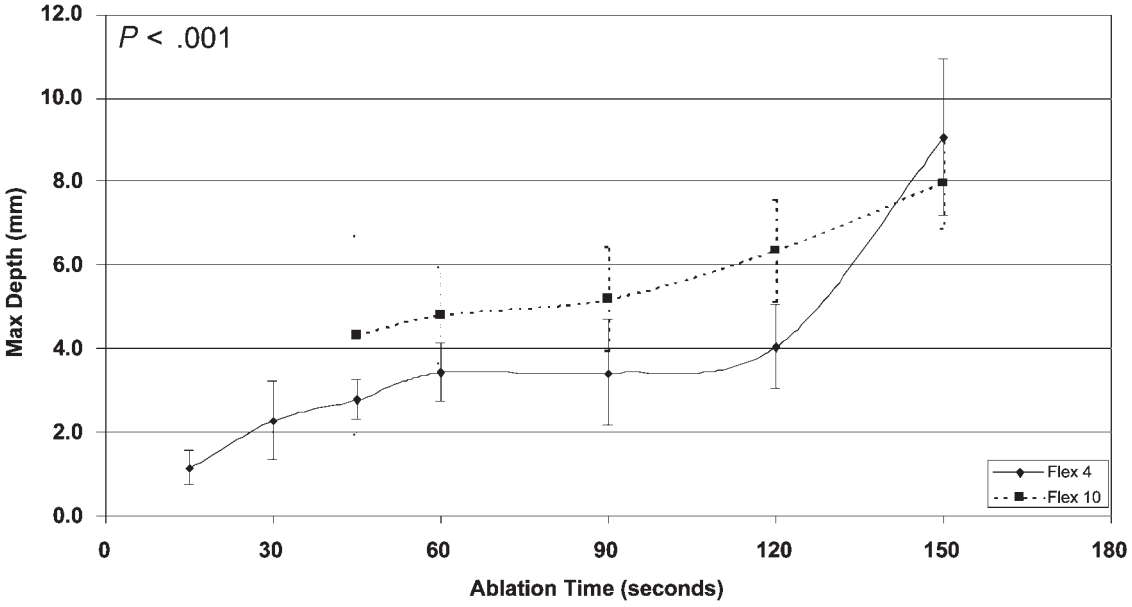

Figure 5. Maximum lesion depth versus time for the FLEX 4 and the FLEX 10 devices. Maximum lesion depth was significantly deeper for the FLEX 10 device compared to the FLEX 4 device ($P < .001$).

and maintained at 10-15°C. The only previously published study examined excised normothermic hearts [Williams 2002b]. This study revealed that the average ablation depth increased linearly during the first minute of ablation for both FLEX 4 and FLEX 10. A plateau was then reached from 60 to 120 seconds for the FLEX 4, and from 60 to 90 seconds for the FLEX 10 device. However, the average ablation depth continued to increase after the plateau phase. The FLEX 10 device was capable of producing deeper lesions than FLEX 4 for the same output power and ablation time. This was

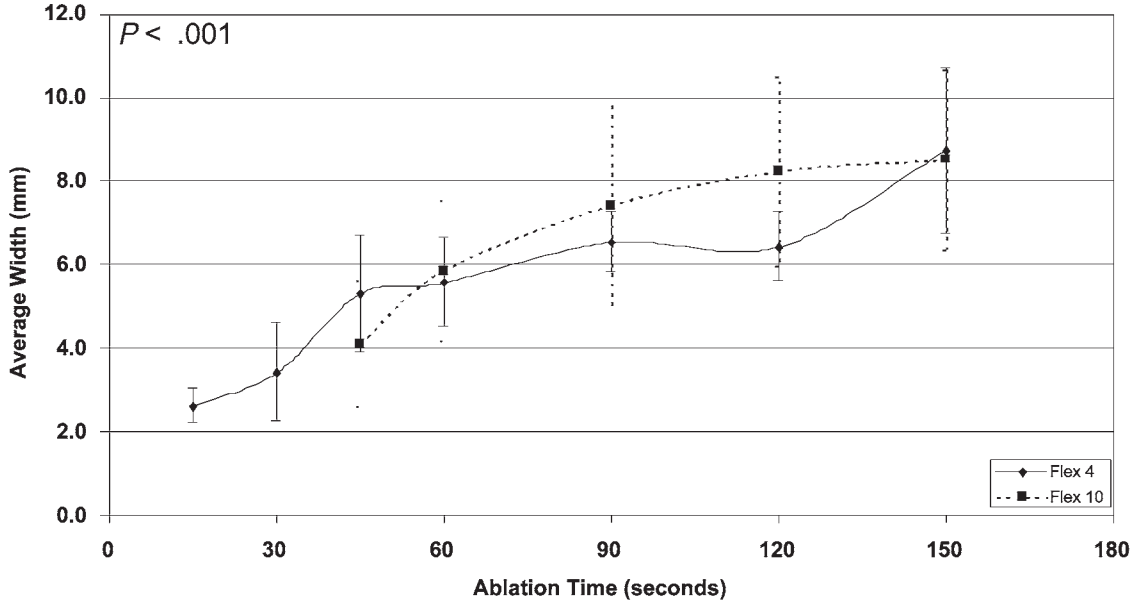

Figure 6. The average lesion width versus time for the FLEX 4 (solid line) and FLEX 10 (dotted line) devices. Lesion width was significantly wider for the FLEX 10 device when compared to the FLEX 4 device ($P < .001$).

expected, since the length of the FLEX 10 microwave antenna was shorter than the FLEX 4 (26 mm vs. 40 mm). This resulted in a higher density of microwave energy within the tissue, and therefore deeper lesions. It is not well understood, however, why a plateau is reached during the ablation. Williams and colleagues also identified a similar plateau phase while investigating dosimetry for the Flex 2 microwave device [Williams 2002b]. It was hypothesized that by averaging and plotting the lesion depth data may have contributed to the plateau phase of the graph. However, a plot of the maximum lesion depth versus time was done for both the FLEX 4 and the FLEX 10 devices. The shape of the dosimetry curves produced was similar to that of mean lesion depth versus time for both the FLEX 4 and FLEX 10 devices. This leads to the conclusion that the plateau phase of the curves are characteristic of the devices. The non-uniformity of the Specific Absorption Rate pattern (SAR) created by the microwave applicator within the tissue and a modification of the microwave absorption properties of the myocardial tissue with the temperature would be another hypothesis to investigate in order to explain the occurrence of continued lesion growth after the plateau phase.

Study Limitations

The use of TTC staining technique for identifying infarcted tissue is sensitive, reliable, and cost effective [Adegboyega 1997]. The method used for determining lesion width and depth, though accurate, may have been affected by observer error. However, a caliper set at 5 mm was photographed along with the tissue sample and this was used as a reference of measurement in an attempt to reduce error. At higher settings (90 to 150 seconds) there was some amount of tissue shrinkage, which may have caused an underestimation of tissue depth. A final shortcoming of this study was that it was performed in normal porcine hearts. These findings may not be fully comparable to diseased atrial tissue as seen in the clinical situation.

In summary, the dose–response relationship of the FLEX 4 and FLEX 10 microwave devices were successfully established. The curves were predictable and reproducible. Atrial ablations revealed that both devices were capable of producing transmural lesions on the cardioplegically arrested heart at 65 W. An understanding of the dosimetry of these microwave devices will not only help to ensure transmurality but also help in reducing the risk of collateral damage to vital structures [Manasse 2003].

ACKNOWLEDGMENT

Supported in part by NIH grants 5R01 HL32257, T32HL007776.

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