genii® gi 4000

August 2012

White Paper: Argon coagulation tissue effects using pre-clinical data comparing the Genii® *gi 4000* and the Erbe VIO300D/APC2 electrosurgery generators

Genii *gi4000*

Erbe
VIO300D/APC2

Background

The Genii *gi4000* was cleared by the FDA for sale in the US on March 22, 2012. To date, it has been used in the electrosurgical treatment of more than 75 patients for routine to complex polypectomy, EMR, biliary and pancreatic sphincterotomy, monopolar and bipolar contact coagulation and multiple argon coagulation indications. It has demonstrated safety and efficacy. (More information about the *gi4000* is available in the White Paper, "Technology Overview and Pre-Clinical Data, Genii *gi4000* Electrosurgery Generator" which reviews the features and benefits of the *gi4000* and includes third party pre-clinical data comparing the *gi4000* to the first generation Erbe ICC200/APC300 unit in all output modes.)

US FDA cleared Jan 8, 2003, the VIO300D/APC2 (second generation) system from Erbe (Erbe Elektromedizin GmbH) is widely used in US endoscopy centers. The APC2 was the first system introduced to the US with an amplified argon beam characteristic. (Manner 2005) The amplified constant beam is called the "Forced" mode. Additionally the system offers a precise mode, and two speeds of pulse modes. A comparison of the amplified Forced Mode to the non-amplified ArC Smart™ mode of the *gi4000* is the subject of this current white paper.

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Study Protocol

Data was gathered and reviewed in total by three researchers and one EE engineer: one PhD, one MD gastroenterologist, and one MS, all with experience in the methodology. The study was funded by Genii, Inc. and was not blinded. Ex vivo protocol using porcine liver, separated into similar size gross sections, and placing injury activations similar to Johanns (1997), Watson (2000), Norton (2002), and Manner (2005) was followed. An Erbe VIO300D/APC2 was used with 2.3 OD Erbe straight fire FiAPC probe #20132-214. The *gi4000* was operated with one ArConnect, #G11-200-31 and one Erbe straight fire 2.3 OD standard probe #20132-166. Probes chosen were those compatible with each generator and are believed to have identical firing properties. All activations used fresh Genii single grounding pads ref #G11-200-31. Each generator/argon unit was set to deliver 1 liter/min argon gas. The flow rate was not varied (van Swol 1998). For each activation an experienced researcher, aided by either the MD or PhD, used a ruler in an attempt to keep the probe distance from the tissue as constant as possible at 4mm.

Three injury spots for each power setting between 15 and 90 watts in five watt increments were made. All comparison activations were timed to a constant one second. A total of 48 spots for each generator was possible. Phase three of the study consisted of making three spots at power settings from 30 watts to 90 watts at 10 watt intervals with an activation of two seconds time, with the *gi4000* only.

Measurements were made in millimeters, rounded to the nearest hundred (0.00) using a General No. 147 electronic caliper, accurate +/- to 0.02 mm. The caliper was re-zeroed between each three measures. All diameter (width) measures were made across the widest portion of each lesion. All lesions were quite uniform in circularity. After diameter measures were made, the lesions were bisected with a sharp scalpel and the two halves spread. The depth of the eschar was measured at the deepest point—usually the center. All lesions were similarly elliptical in cross section.

All measurements were made in duplicate using a pre-prepared printed Excel summary sheet and manual ink mark, and also entered into the corresponding Excel sheet on a lap top computer. (Dell Inspiron). Photographic records were made periodically during the study. For reporting, each measure was conserved as a discrete unit. In addition, the three lesions in each set were averaged. All averages for each type (diameter or depth, etc.) were then averaged to give a summary average. No statistics were attempted, so no claims of significance are made.

A portion of the study sought to measure the effect of increasing power on the arc distance (or arc length) of each system. Arc length is an important clinical parameter because the current prevailing theory of perforation in clinical gastroenterology with argon coagulation is that 'touching' the tissue with an active probe increases the probability of clinical perforation.
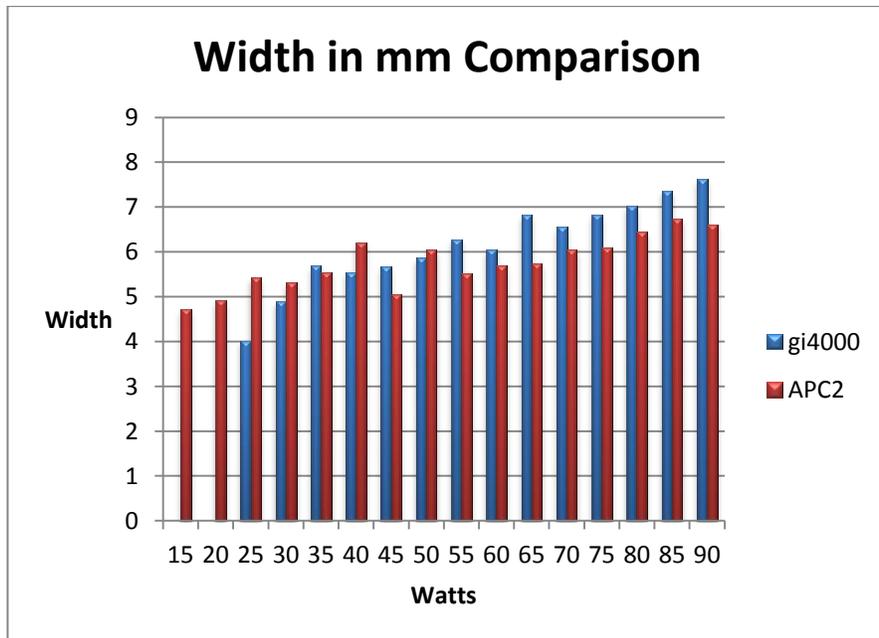
Results

Considering similar protocols previously cited, all results were comparable or reasonable to sizes of lesions measured in previous publications. The amplified character of the VIO300D/APC2 was evident in the results of depth measures as expected. Also as expected, the non-amplified character of the *gi4000* ArC Smart™ beam did not produce a plasma beam adequate for clinical use at power settings below 25 watts. This unit is marketed with instructions contraindicating settings below this threshold. The diameter range over all power settings for the *gi4000* was 3.82mm (activation one at 25 watts) to 7.99mm (activation two at 90 watts). The diameter range for the VIO300D/APC2 over all power settings was 4.51mm (activation one at 20 watts) and 6.97mm (activation one at 85 watts).
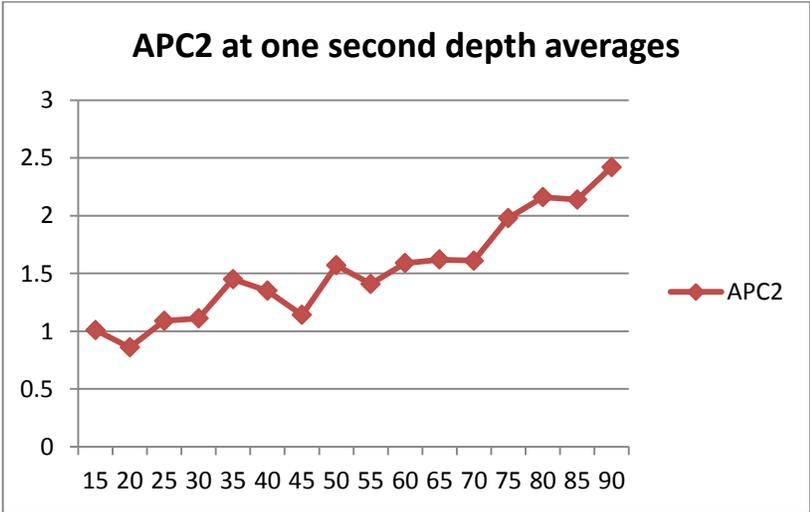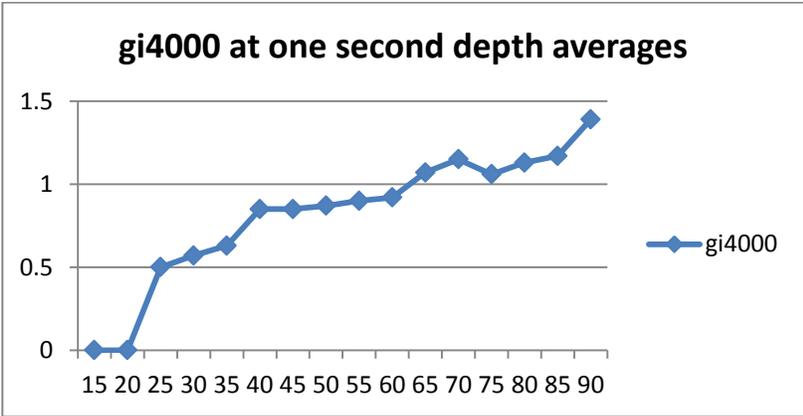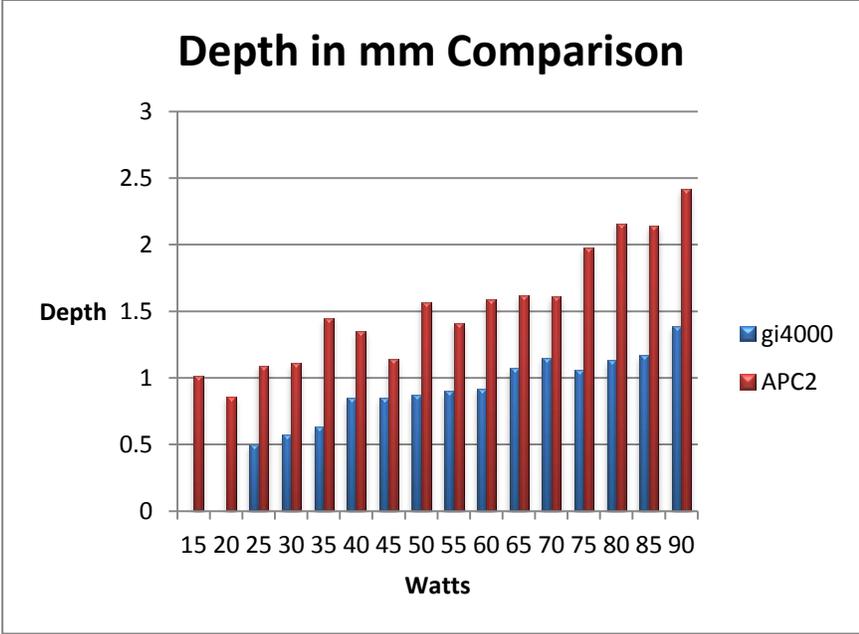
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The depth range at one second, over all power settings for the *gi4000* was 0.4mm (activation two at 25 watts) to 1.55mm (activation one at 90 watts). The depth range for the VIO300D/APC2 over all power settings was 0.83 mm (activation two at 20 watts) and 2.47mm (activation three at 85 watts).
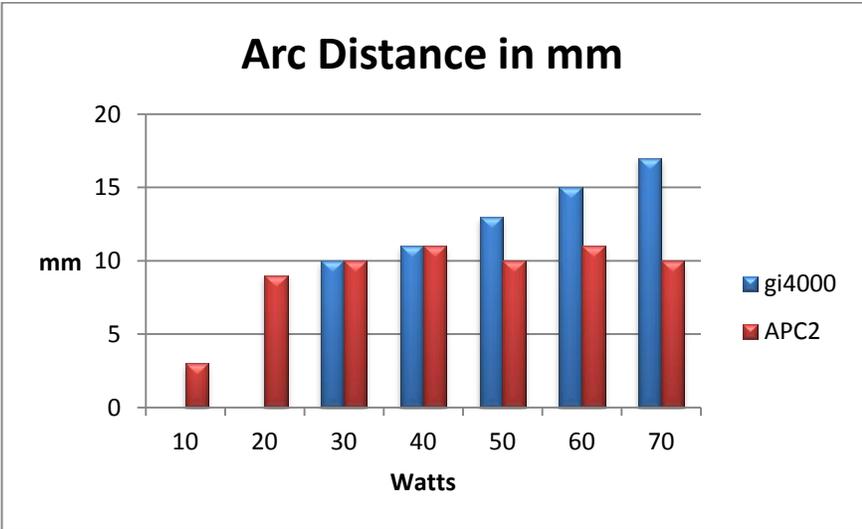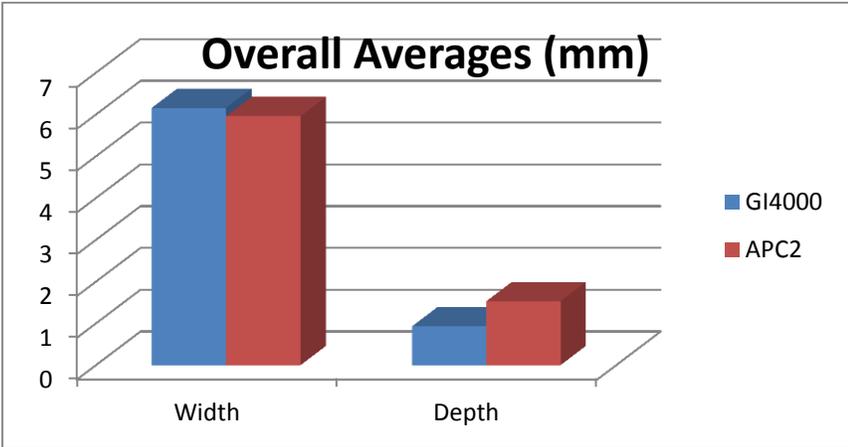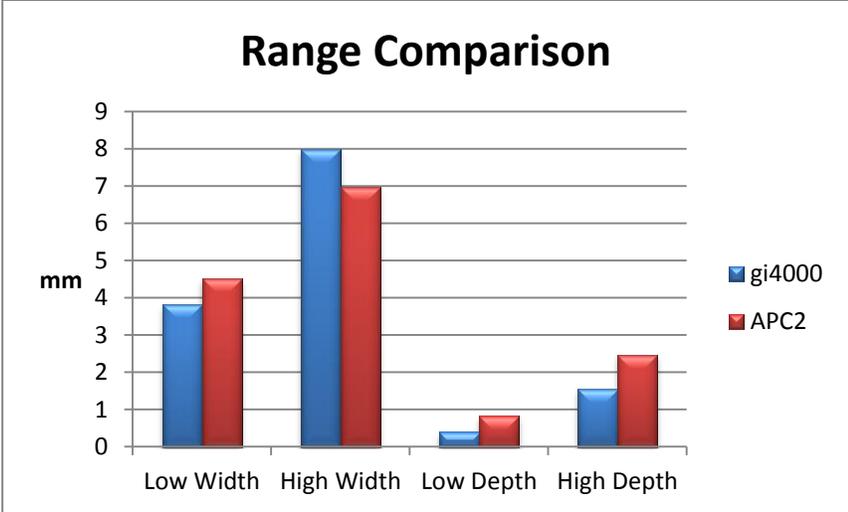
The overall summary averages at one second were: VIO300D/APC2 diameter 5.76mm and depth 1.53mm. *gi4000* diameter summary was 6.16mm and depth 0.93mm. The *gi4000* therefore showed overall a 7% larger total average in the diameter of lesions, while the VIOAPC2 showed an overall average depth of injury 65% greater than the *gi4000.*
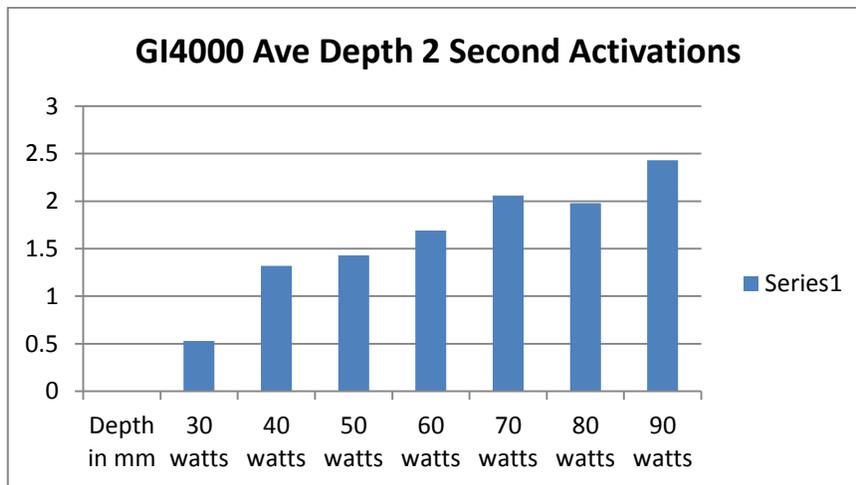
The diameter range over seven power settings at two seconds for the *gi4000* was 5.94mm (activation one at 30 watts) to 9.00mm (activation two at 90 watts). The summary average for diameter at two seconds was 7.09mm. The depth range at two seconds, over seven power settings for the *gi4000* was 0.78mm (activation two at 30 watts) to 2.58mm (activation one at 90 watts). The summary depth average at two seconds was 1.64mm. The one individual lesion maximum VIOAPC2 depth of 2.47 at one second time is near the one individual lesion maximum depth of 2.58 for the *gi4000* at two seconds.

Argon's activation into a current conducting plasma is known to be a threshold phenomenon. In the arc distance portion of the study, the *gi4000* did not produce a stable plasma beam at either 10 or 20 watts, but immediately at 30 watts a stable arc of 10mm (1 cm) was recorded. The arc distance increased steadily with power settings to 17mm (1.7cm) at 70 watts. The VIO300D/APC2 produced a fairly stable beam of 3mm at 10 watts, a 9mm beam at 20 watts and briefly reached a maximum of 11mm at 40 and 60 watts, with 10mm at 70watts. A reliable 10mm (1cm) to 11mm seems to be the arc limit for this unit.

Depth in mm Comparison

gi4000 at one second depth averages

APC2 at one second depth averages

Range Comparison

Overall Averages (mm)

Arc Distance in mm

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GI4000 Ave Width 2 Second Activations

GI4000 Ave Depth 2 Second Activations

Literature review

Since argon capable electrosurgical systems used for open surgery were adapted for use in the gut in 1997, multiple ex vivo and in vitro studies have been published attempting to clarify the tissue effects expected of this modality. Usual protocols attempt to vary the gas flow rate, the power setting, the distance the probe tip is from tissue, the time of activation and the design of a selected generator/argon system. C.F. van Swol demonstrated definitively (van Swol 1998), and clinical use has since verified, that varying the flow rate of argon gas has no effect on tissue coagulation. As long as there is ample argon gas present to support adequate ionization, additional gas is unnecessary and may contribute to the risk of distension, pneumatosis, emphysema and possibly perforation (Norton 2002, Manner 2008, Rey 2010). While unlikely in the gut, gas flow has been cited as a risk factor for embolism in open surgery. When using argon coagulation therapy in the gut, adequate argon is usually present at flow rates between .6 and 1.2 l/min. 2 l/min is usually considered a maximum. When using argon coagulation therapy in the lung, gas flow rates are commonly limited to between 0.3 and 0.5 l/min.

As an anatomic benchmark to relate tissue studies to depth of clinical injury, the gastric wall is considered thickened if greater than 3.6mm and especially if greater than 4mm (de Tejada 2012).

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Farin and Grund described the technology as applied to endoscopic applications in 1994 and stated that tissue injury depth with argon coagulation would be limited to 1-3mm.

In 1997, Johanns et all conducted in-vitro studies to investigate the depth and diameters of tissue coagulation in fresh operative specimens from the stomach, small intestine and colon. Five power/gas flow settings between 40 and 155 watts and 2 to 7 l/min were employed. Application time was varied between 1 and 10 seconds. Angle of the probe to tissue was also varied. The maximum depth of necrosis was measured at 2.4mm and the maximum diameter was 11mm.

Watson et al, published in 2000 a study using the first generation (non-amplified) Erbe ICC200/APC300 system. Arc distance was also measured at various power settings. An arc distance of 1mm at 25 watts was observed, with a 2mm arc at 30 watts. "Power settings up to 99watts did not produce a coagulation ark(sic) at probe tissue separations of 3mm or greater." Tissue effects were studied on three fresh esophageal and three fresh gastric resection specimens using power settings of 40 to 99 watts, using durations of 1 and 3 seconds. Results recorded significantly greater damage to gastric tissue using a 3 second compared to a 1 second pulse. 1 of 42 esophageal samples and 2 of 42 gastric samples showed damage extending into the muscularis propria.

Norton et al reported in 2002 using living swine colon exteriorized with the swine under general anesthesia. All lesions were created with the probe held perpendicular and at 2mm from the tissue, and using the Erbe ICC200/APC300. Flow rate was kept constant at 1.2 l/min. Power settings of 45, 60 and 75 watts were used with times of application of 1, 2, or 3 seconds. Norton noted a non-significant trend toward increased surface area with increased duration of burn. The effect of power setting on depth of injury was consistent across time and vice versa. Circular muscle injury correlated with power, time and total energy delivered. Deeper longitudinal injury was associated with time and total energy, but correlated poorly with power. The authors discussed the intuitive observation that power and duration sufficient to debulk tumors with argon plasma coagulation may raise the possibility of transmural damage when attempting superficial coagulation.

Manner and May (2005) presented the first abstract comparing the new "more powerful" Erbe VIO to the Erbe APC300 system and to Nd:Yag laser. Their study employed porcine liver, but only the two VIO pulsed modes (1 and 2) were compared to the constant APC 300 beam. They reported that with increasing power settings from 30 to 120 watts the VIO produced increasing maximal tissue coagulation depth from 1.5 to 4mm with an application time of 2 seconds, and increased depth to 2.5 to 6mm at 5 seconds. The maximal diameter increased from 8 to 13mm at time of 2 seconds to 10.5 to 15mm at 5 seconds. "Using a power setting from 30 to 60 watts and an application duration of 2 seconds, VIOAPC caused a maximally 100% higher maximal depth of coagulation compared to lesions caused by Nd:Yag laser (2.3mm vs 1 to 1.5mm). In comparison to the APC300 system, maximal coagulation depth was significantly higher and maximal diameter was significantly larger." They anticipated the VIOAPC would replace Nd:Yag for tumor debulking. In 2006, the same authors reported the same conclusions after use on 215 patients, referring to the "high power argon plasma coagulation system."

In 2007, Eickhoff et al reported a prospective study evaluating the APC2 "with amplified power" in pulsed and forced modes. He cited that the first generation APC 300 system produced a plasma arc that destroys tissue to a depth of approximately 2-3mm, and stated that destruction depth with the new amplified VIO increased the depth of injury to 5 to 6mm when power settings and time are increased.

In 2007, Goulet and Disario et al, using an in vivo porcine colon model studied the amplified VIOAPC2, but only reported results of pulsed modes. They noted that muscularis propria injury occurred in 22% of lesions with 10 watts, 62% of lesions with 20 watts, and 86% of lesions with 40 watts. Muscularis propria injury occurred in 42% of lesions at one second of time. Pulse 2 (the faster mode) was shown to deliver the deepest tissue injury, especially at higher powers.

In 2008 in a Current Opinion in Gastroenterology, Manner summarized the effects of the amplification of the VIOAPC2 argon beam in stating that it produced effects "30 to 50% higher compared with the ICC200/APC system and cautions that lower power settings should be used during clinical application in "order to avoid complications such as perforation."

Conclusions and Discussion

Genii had two goals in designing the argon portion of the *gi4000*: First, to make argon coagulation more available by shrinking the size of the unit, thus making it easy to place on booms and travel carts, and by lowering the cost. Second, to improve the performance and safety of argon coagulation therapy in flexible endoscopy. The first goal has clearly been met and embraced with acclaim. The second remains to be proven. Randomized clinical patient studies must follow to confirm Genii's pre-clinical findings from tissue and live porcine studies. Genii hoped to improve safety in the design of the ArC Smart beam first by increasing the arc distance at given power settings, and secondly concurrently make the tissue effect constant, predictable and skewed to superficial hemostasis and coagulation rather than aggressive tissue ablation. The current study data seems to confirm that these goals have been met.

Perforations are not reported when tissue or animal studies are done in controlled laboratory settings. However, it is known that perforations do occur when using argon coagulation in a clinical setting. The mechanism of perforation has not been proven, but current theory postulates that the risk of perforation increases when operators 'touch the tissue' with an argon probe that is actively delivering both gas and heat. Clinicians are well warned of this danger, but find it very difficult to avoid 'touching' in real clinical settings when tissue is moving and arc distances are very small.

The second generation Erbe VIO system is considered to have a better arc distance characteristic than the earlier APC300, but achieved this with an amplified power characteristic that greatly diminished the proportion of tissue injury that is gentle and superficial and skewed the power/tissue effect curve far into the ablation zone at even low powers and short activation times. Additionally, Erbe introduced pulsed modes which have been shown to produce frequent pain and neuromuscular stimulation. (Manner 2008 "Current Opinion", Manner 2008 "Two Center", Eickhoff 2008). Available data is sparse for Forced mode, but both pulsed modes are thought to be more aggressive than the Forced mode, with Goulet and Disario noting that the faster, Pulse 2 mode produced the deepest thermal injury. (Goulet 2007)

In this Genii study, only one depth average produced a lesion less than 1mm deep with the VIOAPC2: 0.86mm at 20 watts and one second. The *gi4000* did not produce a lesion average over 1mm until the power reached 65 watts with a 1.07 average depth. Even at max 90 watts and one second, the *gi4000* average depth did not reach 1.5mm, while the VIOAPC2 had 8 of 16 watts settings produce injury depths greater than 1.5mm. This study measured only the less intense "Forced" mode of the VIOAPC2.

Genii technology has attempted to increase the arc distance, while maintaining the superficial tissue effect quality. A large percentage of argon coagulation therapies in daily clinical practice require

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superficial, gentle hemostasis. The ArCSmart beam character of the *gi4000* gives physicians ample opportunity to achieve this superficial effect. A dispersed wider diameter lesion also aids in creating this homogeneous effect while producing good hemostasis.

Even so, by increasing the power setting and applying power at increasing amounts of time, the *gi4000* ArC Smart beam can also provide sufficient tumor debulking. As shown in the preliminary data, the depth effect is predictable and linear with increased power and time. This predictability makes depth control by the physician easy by simply increasing power setting and time of application.

The ArC Smart beam also employs a unique leakage cancelling feature that attempts to reduce interference with video endoscopy systems. Since the *gi4000* is the first argon coagulation system ever designed exclusively for flexible endoscopic applications, the technology can be focused on these goals. Increased arc distance while preserving limited tissue necrosis will likely be shown to benefit flexible endoscopic argon coagulation treatments.

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