Thermochemical Ablation: A Device for a Novel Interventional Concept

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Solid focal and oligometastatic malignancies are appropriate targets for minimally invasive ablative procedures. Thermochemical ablation is an experimental minimally invasive procedure, which exploits certain features of current thermal and chemical tumor ablation therapies. Engineering principles have been used to design a device, which has been research-proven-capable of coagulating tissue through the combination of a thermal and chemical insult. This interventional device completes this assignment by separately guiding the flow of chemical reagents, drawn from auxiliary systems, to a point at the distal tip of an assembled apparatus. At this position, the respective flow-streams converge and undergo an exothermic reaction to produce a heated, hyperosmolar solute, which serves to ablate the targeted tissue. Ex and in vivo studies have confirmed the utility of this device and the physiologic toleration of this interventional concept. [DOI: 10.1115/1.4005785]

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1 Introduction

There is currently significant interest in minimally invasive therapies to treat a spectrum of medical and surgical disease states. Potentially attractive features of minimally invasive procedures include reduced cost, decreased complication rates, less morbidity, and decreased recovery time. Limiting the number and size of incisions accomplishes a reduction in procedural invasiveness. In addition to reduced morbidity, mortality, and decreased cost, there are several other attractive features of minimally invasive therapies. These include the ability to perform procedures on an outpatient basis and their potential application in a wider spectrum of patients including patients who are not surgical candidates. Examples of some procedures that fall under the minimally invasive umbrella include cryosurgery of the kidney or prostate, hyperthermic therapies for ablation, and endovascular procedures.

Interest in minimally invasive therapies has motivated novel methods for treating solid tumors including those of the breast, kidney, liver, prostate, and skin. Tumor ablation is one of these methods. Currently, two main categories exist for this type of therapy: thermal ablation and chemical ablation. Thermal ablation involves the delivery of thermal energy (or extraction of, in the case of cryoablation) to malignantly transformed tissues. Examples of thermal ablative methods include microwave [1–3], radio frequency (RF) [4–6], high intensity focused ultrasound (HIFU) [7], and cryoablation [8–11]. Chemical ablation involves localized delivery of chemicals to tumors by means of an injection device or a catheter. Examples of chemical ablation agents include acetic acid and ethanol [12,13].

There are, however, limitations of current minimally invasive ablation therapies, some of which will be described here. Incomplete tumor destruction based on lack of fine control over ablated volume is a limitation of both RF and chemical ablation. In liver ablation, large tumor size is a limitation of percutaneous acetic acid and ethanol injection due to the large injection volume required and corresponding risk of systemic toxicity [14,15]. The limitations of RF also include the need for general anesthesia, the expense of an RF ablation device and power generator, and the risk of severe complications like hemothorax and burn injuries leading to bowel perforation when using this technology in the liver [16]. Furthermore, RF has a significant risk of recurrence or tissue injury in the vicinity of larger vessels, the gallbladder, or at the liver surface [16].

We believe that limitations of other minimally invasive treatments present an opportunity for innovation. In the present paper, we describe a novel ablation method that we believe has the potential to minimize complications of other ablation technologies as well as having equal or greater therapeutic benefit and technical feasibility. Our proposed method is also expected to be less capital-intensive compared to the methods described above due to inexpensive device materials.

Thermochemical ablation is the term applied to our proposed method. This approach employs the use of two chemical reagents, which upon reacting produce an exotherm capable of thermally coagulating a volume of tissue, principally a malignancy. Acids and bases have previously been studied for their potential use in exothermic neutralization reactions [17–19], but other categories of exothermic reactions, such as oxidation/reduction chemistry have been reported as well [20].

The choice of reagents may be guided to a degree by consideration of not just the exotherm that would occur but also the products of a reaction. Local cytotoxic effects for ablation must be balanced against systemic toxicity. For example, oxidation/reduction chemistry can be very energetic, but often involves extreme conditions or heavy metals. In contrast many acid-base combinations exist that occur spontaneously on mixing and do not involve heavy metals. Other practical issues are general material availability as well as readiness in liquid form for injection and mixing. These factors account for the initial selection of an acid-base combination since the reagents are available liquids and the products are a salt and water. Additionally, the salt may be one that is already present in the body, meaning that toxicity could be handled simply by dilution and excretion. The other product, water, is of course ubiquitous and nontoxic. Based on the above considerations and prior work, we selected acetic acid and sodium hydroxide solutions for the initial test reagents.

The purpose of this paper is to describe the design and implementation of a device created to accomplish the goal of thermochemical ablation. This device is termed a thermochemical ablation (TCA) device.

2 Design Methodology

The initial vision of the TCA device was a configuration, which would facilitate the exothermic reaction of two chemical reagents in which the elevated temperature of the discharged reaction products would enable thermal coagulation of tissue. The hyperosmolarity of the reaction products would be expected to have the added effect of chemically ablating the tissue. The combination of ablation mechanisms in this modality gives rise to the term thermochemical ablation. The minimum requirements that were specified at the initiation of the design process included:

- (A) chemical and thermal stability of device materials
- (B) ability of the device to be deployed percutaneously
- (C) appropriate gauging of device components to allow for reagent flow without compromising the requirement for a minimally invasive injection
- (D) design versatility so that the device may be sized up or down for ablating targets at different anatomic depths.

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Fig. 1 Overall view of the thermochemical ablation device displaying its key operational components

The bases underlying each of these requirements will now be discussed. Requirement (A) was motivated by the knowledge that corrosive reagents have potential application in this ablation technique and that polymeric components of certain potential device materials lack the necessary chemical resilience to avoid decomposition. Requirements (B) and (C), taken together provide for maintaining this ablation method as a minimally invasive procedure. Requirement (D) ensures the anatomic versatility of the device.

3 Design Iterations

Several prototype devices were tested before arriving at the version presented in this manuscript. Initially, the concept of injecting acid followed by base into a singular tissue location was tested. This design provided for an exothermic chemical reaction and accomplished tissue coagulation, but it was found that decreased mixing of the reagents due to sequential injection provided for smaller elevations in temperature as well as the increased risk of unreacted reagent deploying systemically. A second design provided for mixing of reagents at the proximal end of the device, which allowed for increased temperature elevations but included the undesired effect of needle-track heating as the reaction product traveled to the distal end of the device before entering tissue. The third and current version of the device will be detailed below.

4 Device Overview

The description of the TCA device is subdivided into two main sections. The first will display photographs to illustrate the practical implementation of the device. Subsequently, schematics of reagent and product flow within the device will be displayed to convey its functional design.

Figure 1 displays the TCA device in its operational setup and environment. The figure exhibits the individual and shared auxiliaries of the device. The individual auxiliaries are two syringes, which act as reservoirs for the reagents employed in any particular thermochemical ablation. The contents of the syringes are simultaneously conveyed to the ablation device by means of tubing. The shared auxiliary is a syringe pump (left), which is capable of providing reaction product flow-rates from 0.10 to 9.00 ml/min. The distal, tissue-engaging portion of the TCA device is also displayed in Fig. 1 (right) as it pierces the anterior surface of a liver lobe during *in vivo* experimentation.

A vector based drawing of the distal-most section of the device is shown in Fig. 2 (left). It is open-faced so that the internal anat-

omy of the tissue-engaging portion of the device may be appreciated. As pictured, the internal stainless steel lumen with an internal diameter of 0.7 mm has several 0.5 mm diameter holes drilled at its distal tip. These holes allow for mixing of the central with the peripheral flow-streams. The internal stainless steel lumen travels within a distally beveled stainless steel cannula with an inner-diameter of 1.1 mm and an outer-diameter of 1.3 mm. The stainless steel cannula also has holes drilled into its distal tip of 0.8 mm diameter to allow discharge of the heated reaction product into the tissue. The external flow-stream passes over the external surface of the internal stainless steel lumen. The internal and external streams converge at the tip of the device and have begun reacting prior to their entering the tissue.

A simplified device schematic of internal reagent flow at the distal portion of the device is also displayed in Fig. 2 (right). It can be seen from the figure that the two flow circuits are independent as they travel through the device and converge with one another at the distal-most portion of the device. The purpose of this separation is to avoid heating of the device and the needle track it creates within the tissue.

5 Device Details

The design of the thermochemical ablation device includes a number of features that guarantee its proper operation. These details will now be displayed.

The central feature of the TCA device is the separate guidance of chemical flow-streams. Figure 3 depicts reagent-flow through the individual components of the TCA device. Reagents A and B enter the device by means of tubing (not shown) connected to the proximal luer lock fittings labeled in the diagram. The internal anatomy of the device stipulates flow separation in the proximal portions of the device and flow conversion at the distal-most section of the device. This design provides for confinement of heated reaction products to the distal tip of the device and discharge of these products within the targeted tissue.

Figure 4 displays photographs of the assembled and disassembled components of the device. Reagents are directed within three separate components: a polycarbonate rotating hemostatic valve (Tuohy Borst), a distally beveled stainless steel cannula with a proximal luer lock fitting, and a stainless steel inner-lumen with a proximal luer lock fitting (Chiba Needle). The rotary hemostatic valve (O-ring) serves to maintain the position of the stainless steel inner-lumen component of the device by means of compression. O-ring compression is achieved by twisting the proximal portion of the Tuohy Borst clockwise.

6 Device Assembly and Operating Protocol

The first step in the protocol is the selection of two appropriate reagents (i.e., an acid and a base). Step two comprises the fitting of two reagent-filled syringes to an operator-controlled syringe pump. The third step in assembly is completed by attaching the cannula to the Tuohy Borst and inserting the chiba needle as shown in Fig. 4. At this point, tubing may be connected to both luer lock fittings and assembly of the device is complete. The final

Fig. 2 Vector-based drawing of the TCA device tip (left) and schematic flow diagram of the distal portion of the TCA device (right)

Fig. 3 Schematic of reagent flow throughout the entire device as well as labeled device components through which the reagents travel

step in the protocol involves setting the injection volume, flow-rate, and syringe diameter on the syringe pump, according to the experimental conditions.

7 Results

Criteria that confirm success of the design and feasibility of the interventional concept comprise the following:

- (A) quantifiable temperature excursions in excess of those required for tissue coagulation
- (B) thermochemical ablation and the described device can produce quantifiable coagulative tissue necrosis based on histologic analysis
- (C) TCA device can produce approximately spherical lesions in a healthy tissue model
- (D) thermochemical ablation as an interventional concept is physiologically well-tolerated
- (E) evidence that the injection volume does not track through the liver
- (F) evidence that the injection volume does not reflux around the needle.

7.1 Temperature Measurement. The TCA device has been deployed under a range of in and ex vivo experimental conditions. The truest test of the heat-production potential of thermochemical ablation and the utility of the device is in vivo experimentation. In this setting, the presence of blood flow typically provides a strong convective cooling effect referred to as perfusion mediated cooling. Using sodium hydroxide and acetic acid, the current device has been proven capable of producing average tissue temperatures well in excess of 50 °C in porcine liver experimentation in vivo, with maximum temperatures of up to 105 °C having been reached. This is an important point because 50 °C is recognized as the threshold for cell death as a result of thermal insult [21].

Fig. 4 Photographs of the assembled (top) and disassembled (bottom) components of the thermochemical ablation device

Temperature measurements were obtained with a thermocouple inserted at a distance of 5 mm from the device tip. These measurements likely under predict the peak reaction temperature, as temperature in tissues decreases with distance from the device tip as a

Fig. 5 Ultrasound image of the TCA device tip and a temperature probe situated at a distance of approximately 6 mm

Fig. 6 Chart displaying the average change in temperature for a given injection volume and reagent concentration of sodium hydroxide and acetic acid. Measurements were obtained with a temperature probe inserted at a distance of 5 mm from the device tip.

function of the material properties of the tissue and the physical properties of the injection solutions. Figure 5 is an image obtained from ultrasound-guided, device and temperature probe placement during in vivo experimentation.

The main variables affecting temperature are reagent concentration and injection volume. Ex vivo experimentation with sodium hydroxide and acetic acid at concentrations of 5–15 molar and volumes of 1–4 ml produced average increases in temperature ranging from 7.3–43.2 °C. With physiologic temperature at 37 °C, an increase of 20 °C ex vivo would correspond in vivo to a temperature of 57 °C. At this temperature thermal coagulation is nearly instantaneous. Figure 6 shows the general trend was that higher concentrations and greater injection volumes produced higher temperatures.

7.2 Histology. Coagulative tissue necrosis is another necessary endpoint in evaluating experimental ablative therapies. To demonstrate the ablative capacity of the TCA device, in vivo thermochemical injections were performed in porcine livers and the specimens explanted, fixed, and sectioned. To quantify coagulation volumes, computer software was used to obtain measurements of the coagulum on a section-by-section basis. The summation of these measurements was used to calculate the total ablation volume. Typically, resulting coagulation volumes exceeded the volume of reaction product injected by a factor of three or more. For example, the reagents used to produce the images in Fig. 7 were sodium hydroxide and acetic acid, each at a concentration of 10 M. The total volume injected in this case was 2 ml, and the resulting coagulation volume was 6.34 ml. Figure 7 shows a formalin-fixed tissue section (Fig. 7(a)) sided by a view of a fast-frozen tissue section (Fig. 7(b)). Both images clearly show the line of coagulative necrosis. Figure 7(c) displays a hematoxylin and eosin (H&E) stained section of thermochemically ablated tissue with normal liver architecture on the right side of the image transitioning to coagulative necrosis on the left.

7.3 Ablation Volume. As a method of understanding the hyperacute ablation volume produced by in vivo thermochemical ablations, computed tomographic images of explanted specimens were obtained. To achieve this, iodine-based contrast was added to the acid component of ablation reagents prior to exothermic reaction, and liver specimens were CT scanned after explantation. Figure 8 shows a reconstructed image from a representative experiment. This image was processed with Osirix software and provides evidence that the TCA device is capable of producing approximately spherical ablation volumes, acutely in an in vivo model. The provided images also show that reaction products do not reflux around the needle site and do not track through the liver. To analyze acute ablation volumes, Hounsfield unit limits were set from 150 (lower limit) to 1000 (upper limit).

Fig. 7 Formalin-fixed, fast-frozen, and H&E stained histological sections of thermochemically ablated porcine liver. (a) 2 mm formalin-fixed section, (b) 2 mm fast-frozen tissue section, and (c) H&E stained specimen. These images were obtained using sodium hydroxide and acetic acid at 10 M concentrations.

7.4 Safety. Physiologic tolerance of a newly proposed interventional procedure is an absolute requirement. Change in heart rate from baseline is a commonly used vital sign to monitor a procedure of any kind. During in vivo thermochemical ablation experiments using 10 M acetic acid and 10 M sodium hydroxide at a total injection volume of 2 ml, baseline heart rate changed very little in animals undergoing sequential liver ablation. These results suggest that thermochemical ablation in this experimental model is well tolerated.

Safety of the injected solution is another important consideration. Sodium hydroxide and acetic acid are attractive reagents because their product, sodium acetate, is rapidly converted to bicarbonate in the blood, mitigating the issue of systemic toxicity. In fact, given the speed of conversion, measurement of sodium acetate levels in serum poses a significant challenge in clinical chemistry. The salt in this case is also used in formulations for parenteral nutrition [22]. The main potential issue in such an example would likely be the concentration in plasma for whatever portion of the injection eventually became intravascular. However, as perfusion is nearly or completely absent in ablated tissues, the actual acute systemic exposure is expected to be minimal.

Another aspect of safety and toxicity is delivery. The device described in this report is a prototype that is basically a point-source injection system. Future device refinement such as a multi-tined approach analogous to that tested for singular injection solutions like ethanol may provide further control, but until a prospective trial is performed, this remains speculative [23]. With respect to local toxicity, hyperthermic therapies are centered on obtaining adequate margins rather than overtreatment. In cases where an adjacent organ could be at risk, hydrodissection has been used as a

Fig. 8 Osirix image slice (left) and three-dimensional reconstruction of a contrast enhanced thermochemical liver ablation (right)

safety maneuver to increase the distance of the nontarget tissue from the treatment area [24].

8 Conclusion

A number of end points exist for successful advance of novel medical and surgical procedures from the laboratory to the operating room. Loosely, these criteria include the following. At a minimum a new procedure must be as effective as conventional methods of treatment. A new medical procedure should have fewer or less severe side effects than the current treatment standard. Lastly, the cost-benefit ratio of a newly proposed treatment should be taken into account.

The results obtained from initial experimentation suggest the criteria set forth to confirm the initial success of device design and feasibility of thermochemical ablation are met. The TCA device is capable of producing tissue coagulation, similar in many respects to RF and chemical ablation. In an acute animal setting, thermochemical ablation appears to be physiologically well tolerated. It is also possible that side effects from the thermochemical ablation method will be less than those observed in thermal and chemical ablative therapies from the standpoint of risk to adjacent anatomic structures and systemic toxicity. Finally, the device employs the use of inexpensive materials and, thus, has the potential to be a very affordable interventional technology.

Future investigative opportunities for thermochemical ablation may include real-time imaging applications to monitor tissue temperature or lesion formation. In addition, investigation of the molecular mechanism of cell death due to exposure to the hot, hyperosmolar environment produced by this method is an appropriate area of research. Furthermore, experimentation with thermochemical ablation in an in vivo tumor model will be necessary. We believe the research described in this paper provides sufficient evidence for further investigation of thermochemical ablation as a potential interventional therapy.

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