Reducing the extent of tissue damage when using a microwave ablation system to treat heart arrythmias

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ABSTRACT

Background/Aim: Arrhythmia of the heart is common and can be life-threatening. Radiofrequency ablation is a common treatment but arrythmia frequently returns. Animal studies have shown that microwave ablation can penetrate more deeply but causes tiny burns (known as ‘steam pops’). This laboratory study aimed to investigate whether changing atmospheric pressure during microwave frequency ablation, effects occurrence of steam pops and lesion area. **Methodology:** A purposed-built hyperbaric chamber was used to perform microwave ablation on animal heart tissue samples during 10 trials at three atmospheric pressures (0kPa, 100kPa, 200kPa). The number of audible steam pops and lesion size after ablation for each trial were measured using digital measurement software. **Results:** Chi-squared analyses found a statistically significant lower rate of occurrence of audible steam pops at an atmospheric pressure of 200kPa (10%), compared to 0kPa (70%) and 100kPa (60%). Two-sample t-test analyses found mean lesion area was significantly greater at an atmospheric pressure of 200kPa (214.18 mm^3) compared to 0kPa (145.97 mm^3) and 100kPa (147.73 mm^3). **Conclusion:** This laboratory-based investigation found microwave frequency ablation at high atmospheric pressure resulted in decreased steam pop occurrence and increased lesion area compared to lower atmospheric pressures. Future research is needed to test the microwave ablation system in animals and then potentially humans.

Keywords: Ablation, microwave, heart disease, arrythmia, atrial fibrillation, atmospheric pressure

LITERATURE REVIEW

Arrhythmia of the heart

Around the world, over 17 million people die each year from cardiovascular disease. Cardiovascular disease is responsible for around 600,000 hospital admissions and 42,300 deaths in Australia each year (AIHW, 2021). One-quarter of these are due to heart rhythm problems known as cardiac arrhythmias (Priori et al., 2015). This is because the heart pumps blood around the body and if heart tissue is damaged it can cause an irregular heart-beat, known as arrhythmia, which can lead to sudden cardiac arrest (complete cessation of heartbeat) or cardiogenic shock (insufficient blood supply to the body) (Srinivasan et al., 2018). If this occurs a person needs urgent cardiopulmonary resuscitation and/or use of an automated external defibrillator to prevent death (NHFA, 2021).

Current treatments for arrhythmia of the heart

There are three main treatments for heart arrythmias - ablation, an implantable defibrillator, and medications (NHFA, 2021). Ablation is a technique that uses intense heat or cold energy to create tiny scars, or lesions, using radiofrequency electrical signals and restore normal heart rhythm (Figure 1). This is performed by inserting a tiny catheter into a patient's heart via major artery in the leg (NHFA, 2021). A radiofrequency current then passes from the tip of the catheter which causes heating of the surrounding tissue and the small lesion created blocks irregular heartbeats (Ames et al., 2006). Other treatments for arrhythmia include insertion of an implantable defibrillator is a small device that is implanted into a patient's chest and monitors heart rhythm and automatically delivers electric shocks if needed (NHFA, 2021). Medications are also available, and patients are encouraged to follow a heathy lifestyle (NHFA, 2021).

Need for new research

Unfortunately, heart damage is often too deep for usual radiofrequency ablation to reach effectively, and a study found arrythmia returned in 38% of patients who then needed repeated treatment (Marchlinski et al., 2016). Also, implantable defibrillators and medications do not actually fix the underlying problem, patents live with fear of repeated shocks medications often cause side-effects (NHFA, 2021). Therefore, new research is needed to improve heart arrhythmia and this lab-based research project will determine if a novel microwave ablation system can safely penetrate heart tissue more deeply. If successful, the microwave system could then be trialled in animals, humans and ultimately could be implemented to improve the health of thousands of Australians with arrythmia, reduce the risk of hospital admissions (AIHW, 2020) and possibly be used in other areas of medicine such as cancer.

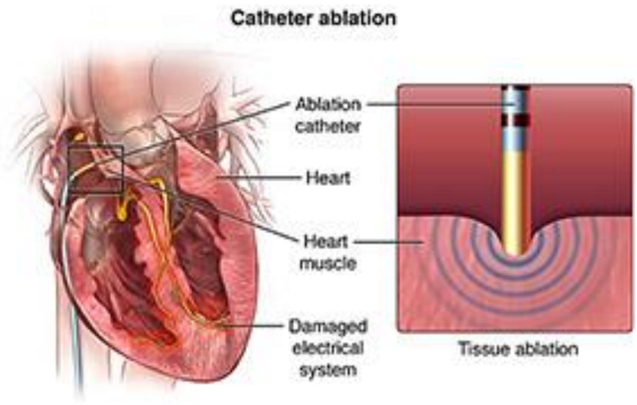

Figure 1: Diagrammatic representation of heart ablation (from The Johns Hopkins Medicine 2022)

Potential of microwave ablation

Microwave ablation offers a promising new heat-based treatment because it can potentially penetrate heart tissue deeper than radiofrequency. This is because microwaves can quickly generate very high temperatures (over 100°C) (Gala et al., 2020) and more deeply penetrate the complex mixture of fibres, fat, and vessels in the heart (Thoracic Key, 2021). An early study involving 10 pigs with liver cancer, found that microwave ablation produced significantly larger areas of ablation (more effective) on tumour size than radiofrequency ablation ($33.3cm^3$ vs $18.9cm^3$) (Qian et al., 2012). These results have recently been confirmed in a systematic review that combined the results from 33 separate liver cancer studies and found that microwave ablation resulted in significantly less progression of tumours than when radiofrequency ablation was used (Dou et al., 2022). Importantly though, liver tumour tissue is very different to the complex fibres and vessels contained in heart tissue (Thoracic Key, 2021).

Communication with internationally renowned cardiologists and engineers (Dr Pierre Qian, Ashvin Bandodkar, Bradman Marks and Tony Barry and from Westmead Hospital and the University of Sydney) highlighted the potential of a new approach to ablation for heart arrythmia. These Australian scientists have recently developed a microwave ablation system and tested it on 15 male sheep (Qian et al., 2015). The team found the microwaves could achieve better ablation depths (Figure 2) than radiofrequency ablation (14.8mm vs 8.0mm) (Qian et al., 2020). However, the microwave ablation also caused 'steam pops' in 21% of ablations (Qian et al., 2020). Steam pops are caused by the explosion of a bubble of steam when ablated tissue reaches a temperature higher than boiling point and this results in tiny burns to the tissue (Haines & Verow, 1990). Therefore, Dr Qian and his Australian colleagues (2020) concluded that microwave ablation has major potential, *but* further laboratory studies are needed to reduce the size and frequency of steam pops. A case report (65-year-old male with heart disease) has also highlighted the need to better understand the effects of steam pops on the heart (Held et al., 2021).

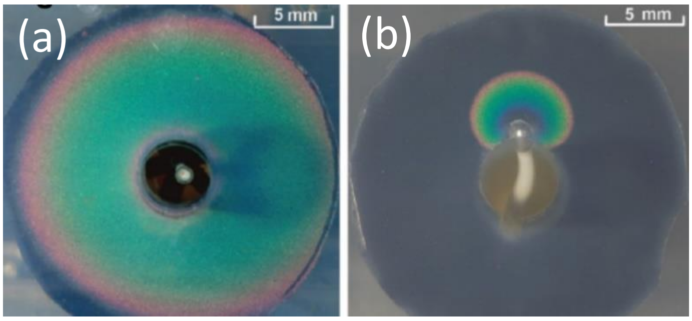

Figure 2: Impact area of heating with (a) microwave (b) radiofrequency ablation (Qian et al 2020)

Potential use of pressure to reduce steam pops

Increasing power using during the ablation has been shown to be ineffective because it was found to speed up the time for steam pops to occur (Mori et al., 2019). One possible strategy for reducing the size and frequency of steam pops is to increase atmospheric pressure via an environment that mimics a 'pressure cooker'. An early study of dog hearts found steam pops are caused when temperatures over 100℃ cause boiling at the catheter tip (Haines & Verow, 1990). Theoretically, ablation could be more performed more safely (less steam pops) at higher temperatures if it was performed in a closed system (or hyperbaric chamber) so that boiling point could be increased (Khan Academy, 2022).

In summary, arrhythmia of the heart is a major health problem and current treatments are suboptimal. Literature suggests that microwave ablation can penetrate heart tissue deeply but does causes tiny burns and hence more laboratory research is needed to determine if changing pressure within the system could improve safety. Significant discoveries in the area of microwave ablation have been made in animal studies but the next stage of research in relation to heart disease is to revert back to further laboratory research. If large ablation zones could be achieved with reduced steam pops, the revised approach could be retested in animal studies before progressing to human trials.

RESEARCH AIM, QUESTIONS AND SCIENTIFIC HYPOTHESIS

This overall aim of this laboratory study was to investigate whether changing atmospheric pressure during microwave frequency ablation, effects occurrence of steam pops and ablation lesion size.

Research Question

Does performing microwave frequency ablation at different atmospheric pressures effect:

i. the number of steam pops occurring in heart tissue and/or;
ii. the mean lesion size of heart tissue that is successfully ablated?

Hypothesis

Alternate Hypothesis

If atmospheric pressure is increased during microwave frequency ablation of animal tissue, the number of steam pops will decrease, and the lesion area will increase.

Null Hypothesis

If atmospheric pressure is increased during microwave frequency ablation of animal tissue, the occurrence of steam pops and lesion size will not change.

METHODOLOGY

This laboratory-based study, using unique phantom tissue models (fresh lamb meat) was conducted at Westmead Hospital under the supervision of Dr Pierre Qian who is a Cardiologist funded by the Heart Foundation. The team also included bioengineers from the University of Sydney (Bradman Marks and Tony Barry). The dependent variables were the number of steam pops and the size of ablation lesion in the tissue. The independent variable for the various trials was atmospheric pressure. Pressures of 0 kPa, 100 kPa and 200 kPa were used. In addition to a zero setting (representing very low atmospheric pressure), 100 kPa was chosen because it represents atmospheric pressure at sea level (Wilmshurst, 1998) and 200 kPa was chosen to represent a high atmospheric pressure where it was considered reasonable to use the pressure a human would experience if scuba diving at a depth 10 m below sea level (Wilmshurst, 1998). Atmospheric pressure during the trials was standardised by using a purpose-built hyperbaric chamber. Control variables included size of tissue samples, ablation power and time, system temperature and microwave frequency. A schematic timeline for the project is provided in Appendix 1.

Procedure

In terms of equipment, a purposed-built hyperbaric chamber was used to perform microwave ablation (Figure 3) on tissue samples (fresh lamb heart meat less than 1 day old) were purchased from a local abattoir and cut with a kitchen knife (guided by a metal ruler) into pieces as close to 2 cm^3 as possible. Sheep heart tissue was chosen because it has similar anatomy to the human heart and has been reported to offer a good animal model for research of the human heart (Di Vincenti, Westcott & Lee C, 2014). Each tissue sample was placed in the hyperbaric chamber, maintained at room temperature, and exposed to microwave ablation supplied by a turntable at microwave frequency of 2.5 GHz for 240 seconds to mimic settings used in earlier animal studies (Qian et al., 2020). Ablation was performed (power = 40 W, irrigation = 12 L/min, impedance = 120-130 ohms). Force was standardised by maintaining the depth of catheter tip insertion (half of the tip) whilst maintaining a perpendicular orientation. A series of 10 trials of ablation were conducted for each of three atmospheric pressures (0 kPa, 100 kPa, 200 kPa) that were controlled by setting the pressure gauge in the hyperbaric chamber (Figure 3).

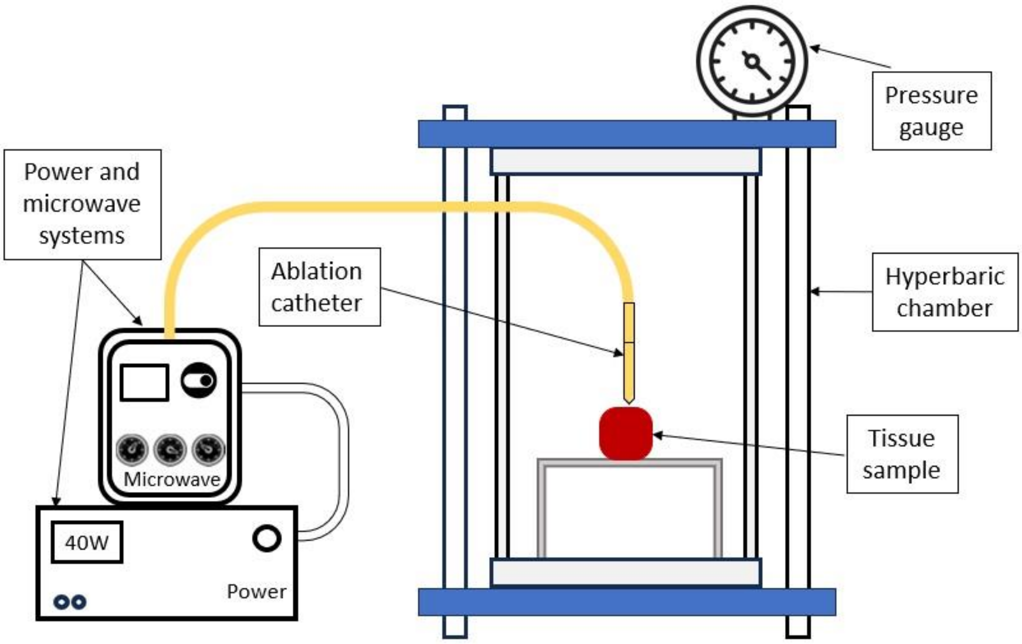

Figure 3: Schematic overview of system setup

Data Collection and Analysis Plan

During each trial, the occurrence of an audible popping sound was manually recorded in a spreadsheet. After each trial, the ablated tissue sample was photographed using a high-resolution digital camera and labelled. These photographs were then uploaded into the scientific image-analysis program ‘ImageJ’ (Version 1.53, 2020), the length and width of each lesion area was measured using the software and raw data recorded in a spreadsheet to the nearest 100th of a millimetre (Schneider et al 2012). Area of each lesion was then calculated using the formula *Area = Length x Width* (mm^2). Number of steam pops at each pressure were compared using chi-squared tests. Mean area (and standard deviation) was calculated for each of the three atmospheric pressures and were compared via two-sample t-tests. Statistical significance was set at $p<0.05$. Microsoft Excel (Version 15.56, 2021) was used for analyses.

RESULTS

The 10 trials at each of the three atmospheric pressures were conducted on a total of 30 pieces of fresh sample tissue with raw data presented in Appendix 2. Table 1 shows the summarised data for steam pop occurrence and mean ablation lesion size. As shown in Figure 4, analysis found a statistically significant lower rate of occurrence of audible steam pops at an atmospheric pressure of 200 kPa (10%), compared to 0 kPa (70%) and 100 kPa (60%). As shown in Figure 5, analysis found mean lesion (ablation) area was significantly greater at an atmospheric pressure of 200 kPa (214.18 mm^2) compared to 0 kPa (145.97 mm^2) and 100 kPa (147.73 mm^2). Table 2 shows visual examples of the tissue samples and other observations made during the trials.

Table 1: Summary results for steam pop occurrence and lesion size

Atmospheric Pressure (kPa)	Steam pop occurrence (%)	Mean lesion size (±SD) (mm^2)
0	70	145.97 (± 0.25)
100	60	147.73 (± 0.44)
200	10	214.18 (± 0.61)

Figure 4: Atmospheric Pressure vs Occurence of Steam Pops

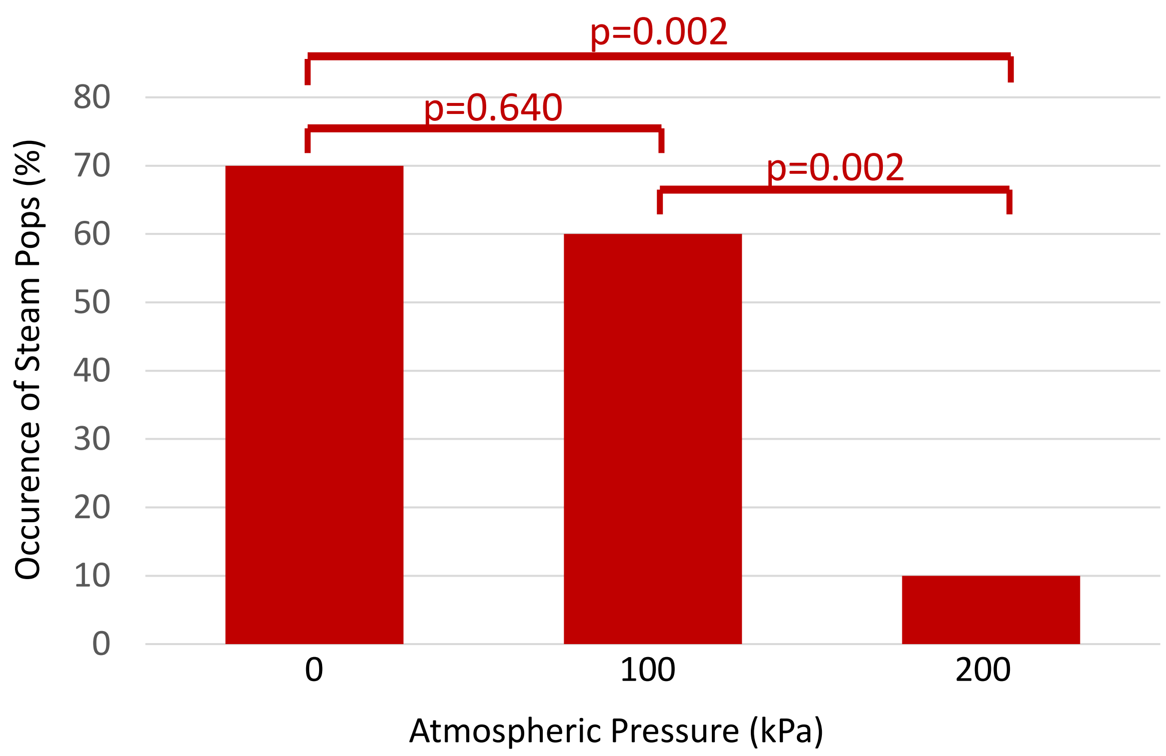

Figure 5: Atmospheric Pressure vs Mean Lesion Area

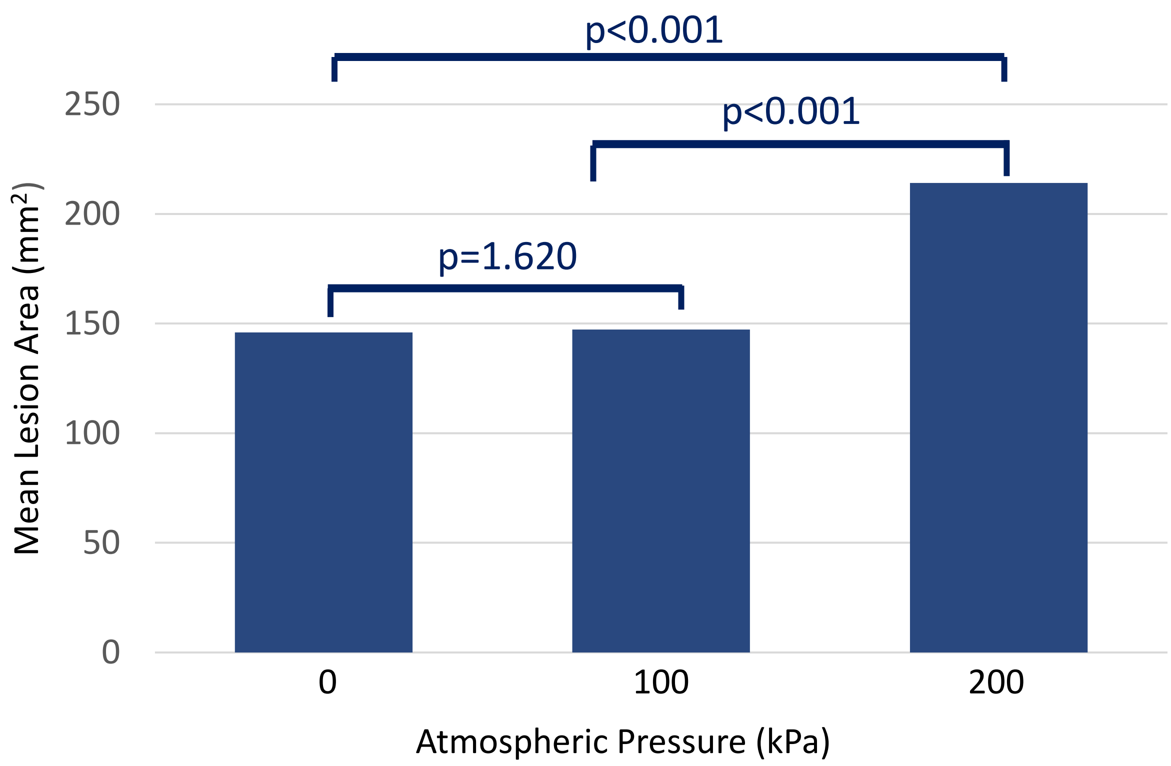

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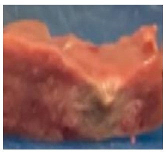
Table 2: Images of tissue samples post microwave ablation and summary of observations made during trials at each atmospheric pressure		
Atmospheric Pressure (kPa)	Example image	Summary of observations made
0		Small and pale lesion area relative to tissue size, very frequent audible popping sound heard
100		Small and pale lesion area relative to tissue size, frequent audible popping sound heard
200		Large and deep area of lesion penetration, very rare to hear an audible popping sound

DISCUSSION

This laboratory-based investigation found when atmospheric pressure was increased to 200 kPa, during microwave ablation of animal heart tissue, steam pop occurrence decreased, and ablation lesion area increased compared to when performed at atmospheric pressures of 0 kPa and 100 kPa. The findings suggest that increasing atmospheric pressure is a potentially effective strategy for increasing ablation area while also improving safety (less micro-burns). This is important because current radiofrequency ablation treatments are typically not long-lasting and Australian and international cardiologists are seeking strategies that allow greater ablation zones without the risk of burns caused by steam pop generation (Qian et al., 2020).

Analysis was used to determine whether the results were statistically significant. Within the methodology, significance was set at $p < 0.05$ (see Data Collection and Analysis Plan). A chi-squared test for independence was run to compare steam pop occurrences and atmospheric pressure because the raw data was categorical. This resulted in a value of $p = 0.64$, when comparing steam pop occurrences between 0 and 100 kPa (see Figure 4). This p value is greater than 0.05 and thus results between these two pressures are not statistically significant. However, a chi squared test comparing 200 kPa with both 0 kPa and 100 kPa (see Figure 4) resulted in a value of p = 0.002, which was below the significance value. A two-sample t-test was run to compare lesion area to atmospheric pressure because the raw data was continuous. This resulted in a value of p = 1.62, when comparing mean lesion area between 0 and 100 kPa (see Figure 5). This p value is greater than 0.05 and thus results between these two pressures are not statistically significant. However, t- tests comparing 200 kPa with both 0 kPa and 100 kPa (see Figure 5) both resulted in a value of $p < 0.001$, which was below the significance value. This means that both steam pop occurrence and lesion area were statistically significantly different at 200 kPa compared to the two lower pressures. Thus, the null hypothesis must be rejected, and the alternate hypothesis was accepted.

Previous studies have demonstrated that the steam pops are caused by 'boiling and popping' of tissue at the catheter tip (Haines & Verow, 1990). Steam pops have been found to be relatively infrequent (1.5% of cases) during radiofrequency ablation (Seiler et al., 2008) but the current investigation is important because it demonstrated that at high atmospheric pressure, microwave ablation produces relatively large lesion size while maintaining a low rate (10%) of steam pops (at 200 kPa). These benefits were achieved at a relatively low power setting which is also important because power has been found to be directly related to the speed of steam pop generation (Mori et al., 2019). However, the rate of steam pops in the present study is greater than would be acceptable in clinical care of patients so further work is needed to ensure safety before moving into human trials. Results of the current study support the theory that increasing atmospheric pressure is associated with a higher boiling point at the catheter tip and therefore achieved a larger ablation area with fewer steam pops (Haines & Verow, 1990). That is, according to the Clausius Clapeyron Equation the boiling point during the 200 kPa trials would be expected to be 20^{o}C higher than during the 100 kPa trials meaning less steam pops would be expected to occur during the same time period. Therefore, the study results support previous research in sheep regarding increased ablation size as a result of microwave ablation (Qian et al., 2020) *but* also improved safety because the higher atmospheric pressure increased boiling point and subsequently reduced the rate of steam pop occurrence.

There were limitations to this investigation, which created a small degree of uncertainty. For example, each tissue sample was not identical in size and shape, and this may have varied the ability of the ablation to penetrate exactly the same for each trial. Each sample was cut using a knife along a metal ruler. Random error of the human eye gave an uncertainty of

±0.3mm (Smith, 2006), and systematic ruler uncertainty was ±0.5mm meaning each cube of meat had a total uncertainty of ±1mm for each dimension. Also, the software ImageJ (Version 1.53) was used to identify lesion dimensions and is accurate to ±0.01mm. An element of random error was present within the investigation because steam pops were recorded based on audible sound to the human ear. To improve this, an electronic sound recording device could be placed within the hyperbaric chamber to identify occurrence of steam pops more accurately.

Within the investigation, sampling bias may have impacted the results, as it was unknown whether tissue samples were harvested from sheep suffering heart arrythmia. As a result, the different tissue samples may have had different probabilities of effectively responding to the microwave ablation. The results were considered precise and reliable because standard deviation was low across all three atmospheric pressures, 0.25, 0.44, and 0.61 respectively (see Table 1). It is difficult however, to evaluate the accuracy of the results, as no known theoretical equations exist for microwave ablation its relationship with steam pops and atmospheric pressure. On balance, the experiment was considered valid because variables were well controlled, meaning the independent variable, atmospheric pressure, was likely the most influential variable. The experimental set-up ensured the control variables were keep consistent via setting system parameters for microwave frequency (2.5 GHz), system power (40 W), and time of ablation (240 seconds). As a result, the results where reliable as similar values occurred throughout each trial under the same conditions and no outliers occurred. A total of 10 trials were run per atmospheric pressure and while trends were observed, more trials could have improved the reliability of results. Further, it is unclear why the difference in steam pop occurrence and lesion size was similar for the 0 kPa and 100 kPa trials, further research is needed to understand these results.

Future research directions could involve studies that aim to replicate the current laboratory results in live animal studies. If results from animal trials could be found to be statistically significant and achieve large ablation areas with a steam pop rate of approximately less than 5%, the animal study could be deemed successful (Seiler et al., 2008). However, trials in the current study were performed using tissue samples from sheep hearts and while these offer a good alternative to human tissue, the samples were not known to have come from sheep hearts suffering arrhythmia. Thus, further research could examine microwave ablation results in sheep with known arrhythmia. If these stages could be overcome, research could then be progressed to human trials and if successful, could be rolled out internationally as a world-leading arrythmia treatment. Importantly, to progress this research to human studies, microwave ablation treatment would need to take place with the patient in a whole-body hyperbaric chamber or treatment room. This technology is available and has been used for providing oxygen therapy (Lam et al., 2017) but further engineering independent research would be needed for viability in relation to heart ablation. Furthermore, while microwave ablation has potential in treating heart arrhythmia, it could also be expanded to other health conditions such as to reduce the size of cancer tumours (Qian et al., 2012).

CONCLUSION

Arrhythmia of the heart is a major health problem and current treatments are suboptimal. Early animal studies found that microwave ablation treatment of heart tissue has potential to increase the area of ablation, compared to usual radiofrequency ablation, but that steam pops were relatively common which made the technique unsafe to progress to humans. The current laboratory-based investigation found when atmospheric pressure, during microwave ablation of animal tissue, was increased to 200 kPa, steam pop occurrence decreased, and lesion area increased compared to atmospheric pressures of 0 kPa and 100 kPa. Therefore, at higher atmospheric pressure, microwave ablation penetrated deeper into the heart tissue without burning and thus reduced tissue damage and was more effective.

Future directions for research include testing the microwave ablation system, at high atmospheric pressure, in animal studies. If effective in animals, the microwave frequency ablation could eventually be tested in human studies where people could potentially undergo surgery in a hyperbaric chamber or treatment room. Ultimately, with more progress and research, microwave ablation could be implemented to treat heart arrythmia, expanded to other areas of health such as cancer and improve the health of thousands of people.

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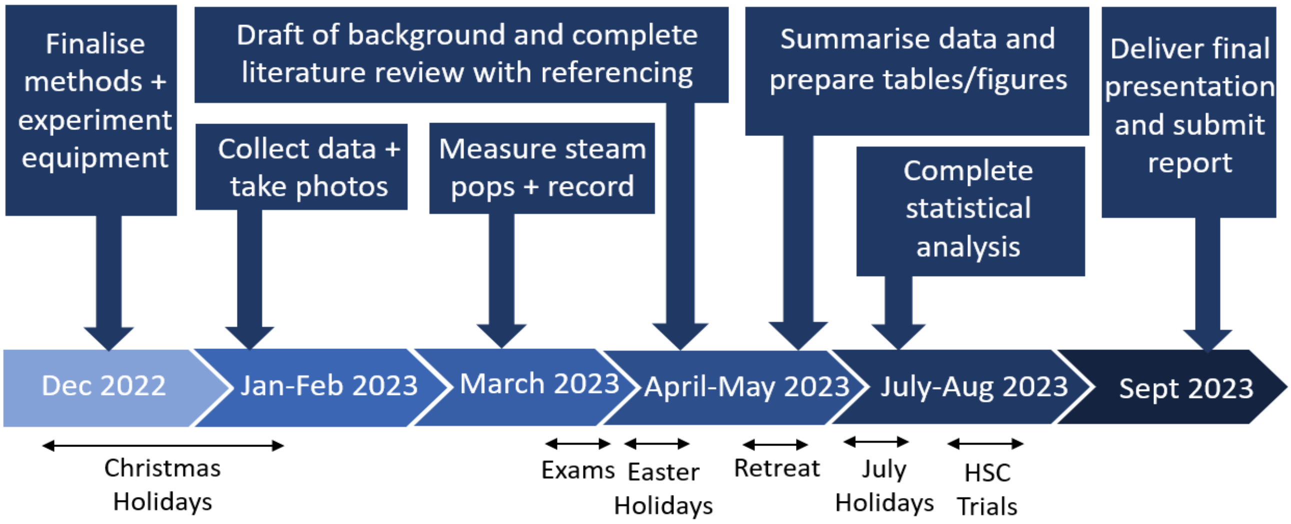
APPENDICIES

Appendix 1: Study timeline



Appendix 2: Raw data collected during the 30 experimental trials

Atmospheric Pressure (kPa)	Power (W)	Lesion width (mm)	Lesion length (mm)	Lesion area (mm^2)	Steam pop (0=no, 1=yes)
0	40	11.34	12.85	145.72	1
0	40	11.23	13.00	145.99	0
0	40	11.36	12.87	146.20	1
0	40	11.22	13.01	145.97	0
0	40	11.21	13.03	146.07	1
0	40	11.27	12.95	145.95	1
0	40	11.40	12.80	145.92	1
0	40	11.34	12.89	146.17	0
0	40	11.26	12.96	145.93	1
0	40	11.31	12.89	145.78	0
100	40	11.52	12.84	147.92	1
100	40	11.55	12.77	147.49	1
100	40	11.59	12.76	147.88	0
100	40	11.49	12.86	147.76	1
100	40	11.50	12.78	146.97	0
100	40	11.60	12.80	148.48	1
100	40	11.51	12.80	147.32	0
100	40	11.50	12.89	148.2	0
100	40	11.60	12.72	147.55	1
100	40	11.58	12.76	147.76	1
200	40	13.60	15.68	213.25	0
200	40	13.62	15.67	213.43	0
200	40	13.64	15.75	214.83	0
200	40	13.57	15.86	215.22	0
200	40	13.51	15.86	214.27	0
200	40	13.73	15.63	214.60	1
200	40	13.65	15.71	214.42	0
200	40	13.59	15.78	214.45	0
200	40	13.68	15.58	213.14	0
200	40	13.75	15.58	214.22	0