NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of high-intensity focused ultrasound ablation for atrial fibrillation as an associated procedure with other cardiac surgery

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2005.

Procedure name

- High-intensity focused ultrasound (HIFU) ablation

Specialty societies

- British Cardiac Society
- British Pacing and Electrophysiology Group
- Society of Cardiothoracic Surgeons in Great Britain and Ireland

Description

Indications

Atrial fibrillation

Atrial fibrillation is the irregular and rapid beating of the upper two chambers of the heart (the atria). It is the most common type of arrhythmia, affecting approximately 0.5% of the adult population[1]. The incidence increases markedly with age.

Atrial fibrillation may be classified as paroxysmal, persistent or permanent. Paroxysmal atrial fibrillation is characterised by repeated self-terminating episodes of arrhythmia that are often initiated by focal triggers within or near the orifice of one or more pulmonary vein. Paroxysmal atrial fibrillation can progress to either persistent

or permanent atrial fibrillation, which do not need focal triggers for initiation and require intervention to restore sinus rhythm.

Patients with atrial fibrillation may be asymptomatic, or they may have symptoms including palpitations, dizziness and breathlessness. They also have an increased risk of stroke as a result of blood clots forming in the left atrium and then embolising to the brain.

Current treatment and alternatives

Non-surgical treatments for atrial fibrillation include medications to control the heart rate, anticoagulants to prevent blood clots forming and electrical cardioversion to re-establish normal rhythm. A surgical treatment known as the Cox maze procedure to treat persistent or permanent atrial fibrillation is usually performed at the same time as open heart surgery for another indication, such as mitral valve disease. Multiple strategically placed incisions are made and sutured to create a 'maze' of scar tissue, which blocks the electrical impulses from travelling through the atrium. A single pathway is left intact for the impulses to travel between the chambers of the heart.

Alternative methods of creating lesions in the atria by ablation have been developed using energy sources such as radiofrequency, microwave, cryotherapy, laser and ultrasound.

What the procedure involves

High-intensity focused ultrasound (HIFU) ablation for atrial fibrillation can be performed with or without cardiopulmonary bypass and is usually performed concomitant with another cardiac procedure. Electrophysiology testing is usually performed before the procedure to identify and map the source of the abnormal electrical signals. An ultrasound device is placed on the outside of the beating heart, and delivers focused ultrasound energy across the wall of the heart. Absorption of the ultrasound energy creates a rise in temperature, which destroys the cardiac tissue within the focal area. HIFU can be used for circumferential left atrial ablation around the pulmonary veins to isolate focal triggers of atrial fibrillation. Additional lesions may be created if required, particularly a mitral line lesion.

There is currently only one HIFU device that is specifically designed for treating atrial fibrillation. The procedure is evolving and research is being carried out on the feasibility of performing the procedure by a minimally invasive approach that does not require open surgery.

Claimed advantages of HIFU ablation include that it is easier and quicker to perform than the Cox maze procedure, destroys focused areas of tissue without affecting surrounding tissues or blood vessels, and may be performed without cardiopulmonary bypass.

Efficacy

Efficacy is based on the results of one case series[2] in which 85% (80/94) of patients were free from atrial fibrillation at 6 months of follow-up. This was achieved in 80% of patients who had permanent atrial fibrillation and in 100% of patients who had intermittent (paroxysmal and persistent) atrial fibrillation. The average time for the circumferential left atrial ablation procedure was 9.4 minutes, during which cardiopulmonary bypass was not required.

The specialist advisors stated that the key efficacy should include normalisation of sinus rhythm, persistence or recurrence of atrial fibrillation; ratio of procedure time to bypass time; atrial transport function; and quality of life.

Safety

Safety findings are based on the results of one case series[2]. Early (up to 30 days after the operation) and late (more than 30 days after the operation) complications were reported, but none were considered to be related to the device or the procedure.

Early complications included bleeding that required surgical exploration 5.8% (6/103); complete heart block 4% (4/103) and sinus dysfunction 1% (1/103), which both required implantation of permanent pacemakers; stroke 2.9% (3/103); and serious deep wound infection 1% (1/103). Late complications included sinus node dysfunction, which required implantation of a permanent pacemaker 2.9% (3/103); ventilation pneumopathy 1% (1/103); delayed cardiac tamponade 1% (1/103); and transient ischaemic attack 1% (1/103).

Mortality at 6 months of follow-up was 5.8% (6/103) in this case series: 3.8% (4/103) early deaths and 1.9% (2/103) late extracardiac deaths.

The specialist advisors stated that the safety of the procedure is uncertain. Theoretical adverse events and uncertainties about the safety of the procedure include how focused the energy is and hence the degree of atrial tissue destruction, any risk of excess myocardial damage (resulting in lack of atrial transportation), any risk of damage to adjacent structures (particularly the pulmonary veins, oesophagus and phrenic nerve) and any increase in surgical risk due to prolonged bypass time (if bypass is required).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high-intensity focused ultrasound ablation for atrial fibrillation. Searches were conducted via the following databases, covering the period from their commencement to October 2005: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1. Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with atrial fibrillation
Intervention/test	High-intensity focused ultrasound ablation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English language articles were excluded unless they were thought to add substantively to the English language evidence base.

List of studies included in the overview

This overview is based on one case series[2] with a short follow-up.

There is currently only one HIFU device available that has been specifically developed for treating atrial fibrillation.

No other studies in humans relevant to the procedure were identified.

Existing reviews on this procedure

A systematic review of intraoperative ablation for the treatment of atrial fibrillation has been published by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S report no. 38, July 2004)[3]. The systematic review did not identify any relevant studies using ultrasound ablation for the treatment of atrial fibrillation.

Practice guidelines for the management of atrial fibrillation have been developed by the American College of Cardiology, American Heart Association and the European Society of Cardiology in collaboration with the North American Society of Pacing and Electrophysiology[4]. High-intensity focused ultrasound ablation was not included in the guidelines.

Related NICE Guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional Procedures:
Interventional procedures guidance documents have been previously issued for the following ablation approaches as an associated procedure with other cardiac surgery: radiofrequency (IPG121), microwave (IPG122) and cryotherapy (IPG123).

In addition, interventional procedures guidance is currently being developed for percutaneous radiofrequency ablation for atrial fibrillation.

Technology Appraisals:
None relevant

Clinical Guidelines:
The first draft clinical guideline for the management of atrial fibrillation has been issued for consultation. This guideline focuses on the medical management of atrial

fibrillation and does not include the use of high-intensity focused ultrasound ablation for atrial fibrillation.

Public Health:
None relevant

Table 2. Summary of key efficacy and safety findings on high-intensity focused ultrasound ablation for atrial fibrillation

Abbreviations used: AF, Atrial fibrillation; FDA, Food and Drug Administration; HIFU, High-intensity focused ultrasound.

Study Details	Key efficacy findings	Key safety findings	Comments
Ninet J et al (2005)[2] Prospective case series (Enrolment Sep 2002 to Feb 2004) Multicentre study (5 centres) Europe (4 countries, not including UK) Device: Epicor Cardiac Ablation System 103 patients with atrial fibrillation (59 male, 44 female) • 76 (74%) permanent AF • 22 (21%) paroxysmal AF • 5 (5%) persistent AF Mean age 66.7 ± 9.4 (43–79) years Mean pre-treatment atrial fibrillation duration = 44 ± 53.1 (6–240) months All patients received circumferential left atrial ablation around the pulmonary veins using an automated cycle; additional mitral line ablation in 35 (34%) patients was done with handheld device Catheter ablation previously attempted in 3 patients Inclusion criteria: Patients with any form of AF present 6 months before operation and already scheduled to undergo concomitant cardiac surgery for valvular correction, ischaemic or congenital heart disease. Exclusion criteria: Acute or active infection; severe heart failure; severe progressive extracardiac disease; prior cardiac operation; presence of previously implanted intracardiac device. 6 months follow-up: Mean 177 (2–232) days, median 185 days Disclosure of interest: not specified	Primary end point of study: feasibility of procedure determined by the time required for sizing, insertion and epicardial ablation using the Epicor device. **Feasibility results** Mean sizing time: 47 ± 39 (9–210) sec Mean device (UltraCinch) size in terms of number of transducers: 10.3 ± 1.4 (8–13) Mean device introduction time: 64 ± 67 (10–360) sec Mean ablation time: 9.42 ± 0.34 (9.27–10.10) min (note: mean ablation of 9.7 min was also reported) The ablation time reflects the time for circumferential left atrial ablation and not for mitral line ablation (if done). **Freedom from atrial fibrillation at 6 months** (assessed by surface ECG and Holter monitoring): 94 evaluable patients: 3 patients excluded as ended study prematurely due to malfunction of the Ablation Control System generator, 6 patients died. According to procedure: • All patients (n = 94): 85% • Patients with additional mitral line ablation (n = 35): 88% According to type of atrial fibrillation: • Permanent: 80% • Intermittent (paroxysmal plus persistent): 100% (note: this was also reported as “paroxysmal AF”) Raw figures were not specified. Note: 2 patients that had atrial flutter at 3 months underwent external cardioversion and remained in sinus rhythm thereafter. Left atrial function assessment was not part of the study protocol, but was reported for 23 patients. All patients in sinus rhythm had left atrial contraction (assessed by presence of transmitral a-wave) at 6 months after operation.	No early or late complications or deaths were related to the device or ablative procedure. The authors stated that “the observed complications and mortality were characteristic in both magnitude and frequency of those commonly observed after cardiac surgery in patients with the same clinical profile undergoing the same concomitant procedures”. 3 patients ended study prematurely due to malfunction of the Ablation Control System generator **Early complications** (≤ 30 days after operation): 20 patients • Bleeding requiring surgical exploration 5.8% (6/103) • Permanent pacemaker required (4 complete heart block, 1 sinus dysfunction) 4.9% (5/103) • Strokes 2.9% (3/103) • Femoral artery embolism 1.9% (2/103) • Serious deep wound infection (sacral decubitus ulcer) 1% (1/103) **Late complications** (> 30 days after operation) (note: article states ≥ 30 days) • Sinus node dysfunction requiring a permanent pacemaker 2.9% (3/103) • Ventilation pneumopathy 1% (1/103) • Delayed tamponade 1% (1/103) • Transient ischaemic attack 1% (1/103) **Mortality** Early deaths: 3.8% (4/103) Late extracardiac deaths: 1.9% (2/103)	The study reports initial clinical results at 6 months of follow-up using the Epicor device. About half (49%) of the patients were ≥ 70 years, with 18% >75 years. Intention to treat analysis was not performed for efficacy analysis. HIFU ablation was done before the concomitant cardiac procedure to avoid additional cardiopulmonary bypass and aortic cross-clamp times. 8 patients received ablation through a minimally invasive approach (5 ministernotomy, 3 limited right thoracotomy). The hand-held device (UltraWand) used for mitral line ablation only became available in the latter part of the study and its use was left to the judgement of the operator. Concomitant cardiac surgery included mitral valve surgery 44.6%, double valve surgery 21.3%, aortic valve replacement 16.5%, coronary artery bypass surgery 6.8%, Bentall operation 6.8%, atrial septal defect closure 2%, ventricular septal defect closure 1% and triple-valve surgery 1%.

Validity and generalisability of the studies

- This overview is based on only one case series with a short follow-up and early clinical experience.
- The study was not conducted in the UK.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr S Furniss, Mr B Glenville, Dr J McComb

- Two specialist advisors described the status of the procedure as being new (first of a new class of procedure, and definitely novel and of uncertain safety and efficacy), while one specialist advisor described the procedure as a minor variation on an existing procedure which is unlikely to alter the procedure's safety and efficacy.
- None of the specialist advisors had performed the procedure before.
- It is a new procedure with unknown safety and efficacy. However, the surgical treatment of atrial fibrillation is well established as effective.
- The procedure is theoretically safe, and it is claimed that the energy source can be applied over blood vessels without damaging them.
- Treatment comparison should be made with the standard maze surgery or the "cut and sew" linear radiofrequency ablation. Microwave ablation or cryoablation may also be used for comparison.

Issues for consideration by IPAC

- A multinational, multicentre clinical trial to assess the efficacy and safety of high-intensity focused ultrasound for pulmonary vein isolation with planned enrolment of more than 30 patients and completion in August 2005 was found in the National Research Register. It is uncertain as to whether the study has completed and the planned date for publication.

References

1 Grubb NR, Furniss S. (2001) Radiofrequency ablation for atrial fibrillation. *British Medical Journal* 322:777–80.

2 Ninet J, Roques X, Seitelberger R et al. (2005) Surgical ablation of atrial fibrillation with off-pump, epicardial, high-intensity focused ultrasound: Results of a multicenter trial. *Journal of Thoracic Cardiovascular Surgery* 130:803.

3 Hazel SJ et al. (2004) Systematic review of intraoperative ablation for the treatment of atrial fibrillation. ASERNIP-S Report No.38. Adelaide, South Australia: ASERNIP-S. http://www.surgeons.org/AM/Template.cfm?Section=ASERNIP_S_Publications&Template=/CM/ContentDisplay.cfm&ContentFileID=1913

4 Fuster V, Ryden LE, Asinger RW et al. (2001) ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *European Heart Journal* 22:1852 –1923.

Appendix A: Additional papers on high-intensity focused ultrasound for atrial fibrillation not included in summary Table 2

No other relevant human studies were identified by the literature search.

Appendix B: Related published NICE guidance for high-intensity focused ultrasound for atrial fibrillation

Guidance programme	Recommendation
Interventional Procedures	**IPG121 Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery** • Current evidence on safety and efficacy appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. • Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of radiofrequency equipment. **IPG122 Microwave ablation for atrial fibrillation as an associated procedure with other cardiac surgery** • Current evidence on safety and efficacy appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. • Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of microwave energy equipment. **IPG123 Cryoablation for atrial fibrillation as an associated procedure with other cardiac surgery** • Current evidence on safety and efficacy appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. • Patient selection and follow-up should be carried out by a multidisciplinary team. Cardiac surgeons undertaking this procedure should have specific training in the use of cryoablation equipment.

Guidance programme	Recommendation
Technology Appraisals	None relevant
Clinical Guidelines	None relevant
Public Health	None relevant

Appendix C: Literature search for high-intensity focused ultrasound for atrial fibrillation

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	Issue 1 2005	21/10/2005
Embase	1980 to 2005 Week 16	19/10/2005
Medline	1966 – April Week 1 2005	19/10/2005
Premedline	April 19 2005	19/10/2005
CINAHL	1982 to April Week 2 2005	19/10/2005
British Library Inside Conferences (limited to current year only)		21/10/2005
National Research Register		21/10/2005

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1. ultrasonic therapy/
2. (high intens$ adj6 focus$ ultrasound).tw.
3. epicor.tw.
4. hifu.tw.
5. or/1-4
6. atrial fibrillation/
7. atri$ fibrillation.tw.
8. 6 or 7
9. 5 and 8