Surgical treatment of atrial fibrillation using radiofrequency ablation

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Histopathology of intraoperatively induced radiofrequency ablation lesions in patients with chronic Atrial fibrillation

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20, 21

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Background: Radiofrequency energy has been extensively used in ablation of arrhythmia but so far no analysis of morphological effects in human left atria has been conducted.

Methods and Results: We studied 58 ablation lesions from 7 patients who had died in 2 to 22 days after open heart surgery plus successful intraoperative cooled-tip radiofrequency ablation to treat chronic permanent atrium fibrillation (4±3 years). Hearts were dissected in relation to performed linear ablations in the atria. Morphology and quantitative transmurality was evaluated in macroscopy and histology. Radiofrequency ablation produces clearly delineated coagulation necrosis (up to a depth of 5.5 mm) bordered by an irregular zone of incomplete necrosis and fresh bleeding even 22 days postoperatively. No superficial charring, thrombotic deposition or perforation was documented. Endocardium and subendocardium display edematic loosening, swelling and microfragmentation of connective tissue fibers. Early after ablation (2 to 6 days) interfibrillar disseminated bleeding and areactive necrosis is found. Later after ablation (21, 22 days) mild inflammatory reaction and granulation tissue can be seen. 24% of all studied lesions – especially in the thick left atrial isthmus (86%) – in patients with documented postoperative sinusrhythm were non-transmural. Nervous fibers with different degrees of thermal injury were detected in the pulmonary vein ostial region.

Conclusions: Intraoperative cooled-tip radiofrequency ablation in atrial fibrillation Results in coagulation necrosis of endocardium, subendocardium and the atrial myocardial layer to a depth of 5.5 mm, bordered by an irregular zone of incomplete thermal damage. Transmularity of the lesions can only be found in 76% of intraoperatively applied lesions. Analysis of acute and mid-term effects (up to 22 days) of intraoperative cooled-tip Radiofrequency to treat chronic atrial fibrillation reveals complete coagulation necrosis of endocardial, subendocardial and myocardial atrial tissue including blood vessels and nervous fibers up to a depth of 5.5 mm. 24% of all abation lesions inside the atria display non-transmural depth especially in the region of the left atrial isthmus. Multiple nervous fibers are documented in the region of the pulmonary veins displaying different degrees of thermal damage. No charring or perforation can be detected in relation to atrial ablation.

Key words: radiofrequency ablation, atrial fibrillation, pathology, histomorphology.

Introduction

Invasive ablation therapy in the left atrium to treat atrial fibrillation (AF) has become engaged in everyday practise of cardiac surgeons and invasive electrophysiologists. Anti-AF surgery has been reported to produce conversion rates as high as 95% depending on duration of atrial fibrillation and enlargement of left atrial dimensions. The original Cox-Maze procedure as a “cut and suture” technique requires high surgical skill. Radiofrequency (RF) ablation as an alternative mode to produce linear lesions has been proposed to facilitate and shorten the procedure. Efficacy has been shown to be comparable to the surgical methods (1-3). Radiofrequency (RF) energy has been extensively used in catheter ablation of Supraventricular and ventricular arrhythmias and effectively creates electrical conduction block. In order to enlarge lesion extent and reduce endocardial carbonization cooled-tip methods have been introduced (4-8). However the pathomorphological alterations induced by RF ablation in human atrial tissue have only been documented in a limited number of case-reports on patients after catheter ablation of different arrhythmia (AV-nodal reentrytachycardia, typical atrial flutter and left ventricular tachycardia). No morphological correlate of left atrial linear ablation in patients with diseased fibrillating atria has been established (9-16). We studied the hearts of 7 patients in whom an intraoperative atrial “Maze-like” cooled-tip endocardial RF ablation had been successfully performed who had died within 22 days.
HISTOPATHOLOGY OF INTRAOPERATIVELY INDUCED RADIOFREQUENCY ABLATION LESIONS IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION

Methods
Out of a total of 145 patients who underwent open heart surgery plus antiarrhythmic procedures using cooled-tip radiofrequency ablation (SICTRA= saline-irrigated cooled-tip radiofrequency ablation) to treat chronic permanent atrial fibrillation patients who died during postoperative hospitalization (7 patients, 2 to 22 days postoperative) were included. The hearts of these patients were studied post mortem and provide the basis of this work. Informed consent was given in all instances. The hearts were excised leaving at least 3 cm. of pulmonary veins to the left atrium. The surrounding tissue including esophagus and mediastinum were studied. In addition any sign of arterial embolism was documented. Postmortem angiography was performed on all hearts and the proximity of any coronary stenoses to the linear ablation lines was evaluated.

1.1. Macroscopy
The atria were opened following the “operative” way via interatrial groove and ritht atrial lateral incision. The right and left atrium was then macroscopically studied and superficial continuity of lesions was documented. Longitudinal preparations of each of the pulmonary vein ostia were performed at different circumferential site (as indicated in figure 3). Lesions traversing the atrium were cross-sectioned as shown in figure 1, histological preparations were performed and the extent of the lesions was documented.

1.2. Histology
The slices of atrial tissue were processed as usual to obtain paraffin blocks. Tissue staining was performed 1. Using Elastica-van-Gieson (EvG) staining and 2. Goldner-staining (Trichrome-Masson staining) to document thermal myocardial damage. Transmurality was estimated based on the findings of myocyte damage in the depth of the atrial tissue. Alterations of vessels (arterial, venous or nervous) in the region of applied RF-lesion were studied. Histological evaluation of lesion transmularity was based on the aspects of necrotic myocardial fibers and was related to the region of ablation and the depth of tissue damage.

Results
A. Patient characteristics
Cardiac surgical procedures performed were mitral valve repair in 2, mitral valve Surgery plus coronary artery bypassing (CABG) in 2, CABG alone in 1, CABG plus mitral, aortic and tricuspid valve surgery in 1 and mitral, aortic and tricuspid valve surgery in 1. All patients had reduced left ventricular function (mean ejection fraction 36±17%) and chronic permanent AF was documented in all patients 1 to 11 years prior to the procedure (mean pre-operative duration 4±3 years). The additional atrial antiarrhythmic operation was restricted to the left atrium in 5 and performed as a biatrial procedure in 2 patients using intraoperatively cooled-tip RF ablation. Linear lesions around each of the pulmonary vein (PV ostia with interconnection lines and two lines from the left inferior pulmonary vein ostial line to the mitral valve annulus and up to the excision of the left atrial appendage were performed (figure 1). In two cases the left atrial appendage was linearly ablated at the transition zon between appendage and left atrium. Applied energy ranged in between 25 to 30 Watts with continuous open saline irrigation (320 ml/h) over a 4 mm. unipolar tip electrode (Medtronic Cardioblante“). Lesions were performed in a stepwise approach ablatin one area until whitish discoloring of the endocardial surface occurred and then moving on (2, 3, 8).

1. Post-operative rhythm follow-up
All 7 patients were in SR or atrial paced rhythm after completion of the cardiac surgery. In 4 cases phases of AF were documented on EKG, in pt. No. 3 and 6 AF was found at day of death. In the five other cases SR was documented on the day of death (table 1). No antiarrhythmic medication was administered (metoprolol 47,5 mg. to 95 mg. once a day was given in all patients).
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2. Cause of death
Patients died 2 to 22 days after the procedure and cause of death was determined during autopsy to be cardiorespiratory insufficiency and pump failure in 3, global cardiac insufficiency and myocardial infarction due to bypass insufficiency in 1, sepsis after pneumonia in 2 and cardiogenic shock in 1 patient.

B. Pathomorphological macroscopy
We studied 58 lesions in 7 patients (8 lesions from the right atrium). No perforation or damage to mediastinal organs was detected. A postmortem coronary angiogram revealed no coronary stenosis in the proximity of any of the linear lesions. Linear lesions distinguished as whitish clearly delineated continuous lines (6 to 13 mm. thick, mean 10 mm.). No endocardial damage was visible during macroscopy and thrombotic formation was absent on all ablation areas (see fig. 1). Charring as a result of endocardial carbonization was not visible on any of the ablation lines. No alterations, luminal narrowing or deformation of the pulmonary vein ostia were seen. All lines were delineated by more or less visible hemorrhagic areas (1 mm.) (see fig. 1). In cross sections ablation lines appeared as clearly demarcated ovoid shaped areas with hemorrhagic bordering zones (fig. 2).

C. Histology
In all histologic specimen ablation areas were clearly visible and delineated. Pattern of thermal tissue damage was comparable in the 7 patients but tissue reactions were different in the 5 patients dying within 6 days compared to the two patients dying after 21 and 22 days. The left atrium (mean thickness 5.4 mm., in between 3 to 10 mm.) was found to be thinnest in the region of the pulmonary veins (1 to 3 mm.), the region of the posterior left atrial wall (2 to 5 mm.) and thickest within the left atrial isthmus (7.4 mm. mean thickness, 4 to 10 mm.). The right atrium consisted of a thinner myocardial layer (mean of 3.8 mm., 3 to 5 mm.).

1. Pattern of thermal necrosis
Thermally induced necrosis of myocardial tissue was documented to include alterations of myocardium, endocardial and subendocardial fibrous tissue, capillary vessels and neural fibers. Complete coagulation necrosis is characterized by rounded, homogenous myofibrillar layers with loss of nuclear staining. Collagenous fibers are fragmented, irregular and show edematous swelling. In the outer margins of the necrotic core different degrees of reduced nuclear staining and loss of longitudinal and cross-sectional striation is seen (fig. 2). The ablated endocardium is acellular without superficial tissie defects. The subendocardial region shows microfragmentation of elastic fibers and edematous swelling of fibrous structures. Acellular, homogenized and sometimes swollen subendocardial fibrotic structures display loosening and widening of the otherwise tight interconnections (fig. 3). Early after ablation (within 6 days) zones of diffuse fresh intramural bleeding with Interfibrillarous erythrocytic infiltrations of the necrotic myocardium were seen. Blood vessels were hyperemic and ectatic, some microvessels depicted thrombotic occlusion. Nervous fibers in the ablation area of the PV ostia show vacuolization and reduced cellular staining as different degrees of thermal injury in about 50% of identified fibers (fib. 3, 4). 21 and 22 days after ablation a granulated tissue rich of ectatic capillaries is found in the outer zones penetrating towards the necrotic core of the ablation area. In the outer layers zones of fresh bleeding from small blood vessels displaying different degrees of wall alterations and thrombosis are found. Only mild inflammatory reaction with removal of necrotic myofibers can be detected in the borderzones around the necrotic cor (fig. 2). Areas with intramural hematoma interrupting the atrial wall configuration were found independent to the time-point of death (fig. 2).

2. Transmurality
Transmurality of a lesion was estimated when complete myocardial necrosis was found reaching up into the epicardial layers (table 2).

A. Pulmonary vein ostial lesions – In these regions with thin myocardial layers complete transmurality was found in all but 1 probe (96%) where a myocardial fiber traversed the ostium insulated by 2 mm.
thick fatty tissue. Myocardial bridges reaching on the epicardial aspect of the PVs can be detected up to 2 tot 3 mm. upon the venous side (tablet 2).

**B. Left atrial and right atrial lesions** – Complete myocardial necrosis can be found up to a depth of 5.5 mm.. An irregular zone of myocardium with reduced nuclear staining and different degrees of loss of transversal striaion margins the complete necrosis. In our preparations incomplete, non-transmural lesions (ranking in between 50% to 80% of myocardial thickness) were found in 24% of all probes (1/28 PV encircling lesions (4%), 0/7 lesions on posterior left atrial wall, 6/7 of left atrial isthmus lesions (86%), 4/8 in the right atrium (50%), 3/7 in the region between left inferior PV and left atrial appendage (43%) and ½ around the left atrial appendage (50%) (table 2, fig. 2).

**Discussion**

This manuscript presents the first morphological analysis of lesions induced by cooled-tip RF ablation in diseased fibrillating human atrial specimen in a series of patients. Whereas macroscopy reveals superficial completeness and no thrombotic apposition or charring, cross sections and histology documents various degrees of non-transmurality. Lesions in the thin myocardial layer of the pulmonary vein ostial region and the posterior left atrial wall almost always produce completely transmural coagulation necrosis. Ablation lines inside the atria revealed a complete thermal myocardial necrosis for a maximum depth of 5.5 mm. bordered by an irregular zone of different degrees of myocardial alteration and disseminated fresh bleeding even 22 days postoperatively. At least one lesion per patient did not show complete transmurality when applying histological criteria (24% of all studied ablation areas).

**Transmurality**

Our findings are in accordance with studies of RF ablation in animal ventricular or atrial myocardium and case reports of patient dying early after ablation. The depth of the lesions depends on convective cooling, electrode tip length and location of ablation. Cooled tip RF ablation is reported to reach up to 7 mm. into the cardiac tissue comparable to our findings. This has practical implications when considering atrial myocardial layers to be as thick as 10 mm. in patients with atrial fibrillation in some areas especially the left (between left inferior pulmonary vein and mitral valve annulus) and right atrial isthmus. In these areas energy delivery needs to be optimized (higher energy output or larger electrode tip) to induce complete transmural lesions (5, 7-18). Even though non-transmural lesions were documented in all patients (from a histological point of view) rhythm success of the procedure was indicated by conversion to SR in all patients with prior chronic permanent atrial fibrillation. No electrophysiologic correlation between histologically non-transmural lesions and electrical conduction properties was made. It still remains unclear how much transmurality in regard to complete tissue necrosis is needed to induce long-term electrical conduction block (12, 13, 17, 18). The high percentage of non-transmural lesions after endocardial linear ablation in the left atrial isthmus is in accordance with reports by the group of Haissaguerre et al. Documenting the need for ablation from the endocardial site and the coronary sinus to produce complete conduction block (19, 20).

**Pattern of thermal injury**

The morphological correlate of RF ablation is constituted of a clearly delineated ovoid shaped necrotic core with complete coagulation necrosis (swollen, rounded, homogenized fibers without stainable nuclei). The subendocardial and intimal tissue show microfragmentation of loosened fibrotic tissue and edematic swelling. Distinctive differences in tissue reaction were found in our study early (up to 6 days postoperatively) and later (21 to 22 days) after intraoperative ablation. Early after ablation areactive thermal necrosis with interfibrillar exposition of fresh bleeding is characteristic. In the region of the pulmonary veins the multiple nervous fibers display different degrees of thermal alteration. Later after ablation (21 to 22 days postoperatively) capillary-rich granulative tissue reaction is documented
on the borders of the necrotic core with mild inflammatory removal reaction. Zones of fresh bleeding sometimes producing confluent intramural hematoma can be detected even after 22 days in the outer border of the necrosis indicating prolonged small vessel wall damage. In close proximity thrombotic occlusion of microvessels was seen. Limited knowledge exists on the morphology of radiofrequency ablation in humans stemming from rare case-reports. One report on ablation in AV-nodal reentry (2 days postinterventional) and one report on a case of atrial flutter ablation (4 months) depict thermal damage on right atrial tissue documenting a necrotic region consisting of myofiber coagulation necrosis. Case reports on thermal ablation of left ventricular myocardium to treat ischemic ventricular tachycardia in a total of 6 patients show dissiminated regions of bleeding lesions reaching up to 7 mm. deep (after cooled-tip ablation). No report on a homogenous series of patients ablated within diseased left atria with permanent atrial fibrillation exists (9-11, 14-16).

The pattern of thermal injury seen in our series of patients is comparable to atrial injury by RF ablation in animals. Coagulation necrosis is characterized by defragmentation and destruction of myocytic contractile apparatus leading to loss of electrical conduction function (5, 7, 9, 10, 13, 17, 18).

In our study fresh bleeding was a universal finding after radiofrequency ablation. These observations can be traced back to the rare documentation of thermal damage to smaller blood vessels in the region of ablation with vessel wall alterations (leakage) and thrombosis on the one hand. The other factor leading to prolonged hemorrhage might be vessel vulnerability in patients with anticoagulant therapy. The coexistence of intramural hemorrhage in ablation areas has been documented in case reports and animal findings without producing severe clinically detectable complications. Further studies to evaluate the effects of radiofrequency energy on vessel function are needed (5, 7, 9, 10, 11).

Anatomy of the pulmonary vein ostial region in regard to atrial fibrillation surgery

In patients treated with intraoperative RF ablation SR usually spontaneously occurs within 6 months after the procedure. This “late conversion” may be in part due to electric remodeling of the atrium. As documented in this study there is a zone of bleeding and incomplete myocardial necrosis around the thermal necrosis core. Over time the diffuse hemorrhagic zones are degraded by capillary rich granulation tissue replacing the necrotic core from the epicardial side. This process may lead to further enlargement of the initial necrotic zone and in this way may lead to complete transmurality later on. On the other hand especially the pulmonary vein ostial regions are rich of nervous fibers indicating a special role in autonomic innervation. Intact neuronal innervation is reduced by ablation procedures hinting at a possible role of autonomic remodeling being another possible factor (in addition to time-dependent post-operative prolongation of atria refractory period and recovery from surgical damage and perioperative ischemia) leading to late rhythm success (2, 3, 8, 21).

Conclusions

Radiofrequency ablation in atrial fibrillation leads to coagulation necrosis of Endocardium, subendocardium and atrial myocardial layers up to a depth of 5.5 mm, bordered by an irregular zone of incomplete thermal damage. No superficial thrombotic deposition, charring or complete demolition of atrial tissue is seen. Intramural fresh bleeding and hematoma may be found even up to 22 days postoperatively.

Transmurality as based on histological criteria can only be documented in 76% of all applied lesions. Especially the thick left atrial isthmus displays different degrees of transmurality after intraoperative cooled-tip radiofrequency ablation in over 85% of our studied patients.

Multiple nervous fibres around the pulmonary vein ostia indicating the special role in sympathetic innervation display different degrees of thermal damage.
Limitations
This pathomorphological analysis was restricted to the patients dying in hospital within the first three weeks after intraoperative cooled-tip RF ablation to cure atrial fibrillation and by this includes only a limited number of patients and lesions. No patients with longer follow-up have been included so no long-term effects of these procedures could be studied. Patients included had different underlying heart disease which may affect the morphology of the atria in AF and the morphological alterations induced by thermal energy.

References


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Table 1 Atrial rhythm as documented on EKG during the first 6 postoperative Days (AF = atrial fibrillation, SR = sinus rhythm).

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<td>left atrial isthmus</td>
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<tr>
<td>pulmonary vein ostium</td>
<td>96%</td>
<td>1 – 3 mm</td>
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<td>posterior left atrial wall</td>
<td>100%</td>
<td>2 – 5 mm</td>
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<td>50%</td>
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Table 2: Wall thickness and percentage of transmural lesions in different regions on the left and right atrium.
Figure Legends

Figure 1
Macroscopic aspect of right (A) and left atrium (B) and schematic view of ablation lines (C and D) after biatrial (view onto repaired mitral valve) intraoperative ablation (female, 67 years) (a to c: sites of histological sample). All lines are surrounded by hemorrhagic zones (->; 1 mm.) (line 1: over the interatrial septum (IAS), line 2: cavotricuspid isthmus, line 3: line from right atrial appendage (RAA) to tricuspid valve (TV), line 4: interconnection line between the two pulmonary vein blocks, line 5: line from left inferior PV (LIPV) to excised left atrial appendage (LAA), line 6: left atrial isthmus line, IAG=interatrial groove used for surgical access to the left atrium, RIPV=right inferior PV, RSPV=right superior PV, LSPV=left Superior PV, SVC=superior caval vein, SC=coronary sinus ostium.

Figure 2
Morphology of ablation area 21 days postoperatively (A) and left atrial isthmus line in the same patient (B to D) (male, 65 years) A. Macroscopic cross section of an ablation line from the right atrium (arrows point at visible extension of necrosis) with clearly delineated lesion (macroscopically 3 mm. deep) by hemorrhagic border. B. Histologic gross section (EvG staining) of the non-transmural left atrial isthmus line with intramural hematoma (*) and necrotic core up to a depth of 4.5 mm.. C. Magnification of panel B: transition zone from complete necrosis (upper part; anuclear myocardial cells, N=necrosis) and partial thermal damage (below; striation of myocardial cells and some nuclei visible=M). D. Magnification of panel B: capillary rich granulation tissue and Removal reaction: ectatic capillaries and intramural bleeding.

Figure 3
Morphology of pulmonary vein ostial lesions 2 days postoperative (A. Macroscopy, B. to D. Gross histological longitudinal view of Ablation zone (gray arrows) in the transition zone between left atrium (left) and PV (right) and magnification from panel D (Goldner staining) (female, 61 years) (*-»=myocardial bridge onto PV) (a to f: sites of histological sampling): A. View of right pulmonary veins with 3 ostia and whitish lesions encircling the pulmonary veins at the atrial side and surgical access via interatrial groove. B. Left inferior PV ostial region. Left atrial myocardial layer extends upon epicardial side of the pulmonary vein (M=left atrial myocardium). C. Left superior PV ostial region with clearly hemorrhagic demarked ablation zone. Fragmented subendocardial tissue and edematic loosening in the ablation zone. D. Right superior pulmonary vein ostial region with hypertrophic, fibrotic left atrial myocardial layer reaching 3 mm. upon the pulmonary vein. Intimal fibrosis within the first cm of the pulmonary vein and completely transmural lesion at the ostial region. E. Magnification of panel D at the end of the myocardial bridge: Intimal tissue (I) with edema and loosening of subendocardial (S) connective tissue.

Figure 4
Histology of PV ostial ablation (Goldner staining; A: gross histology, B: magnification from panel A, male 65 years, 4 days Postoperatively): A. Ostial segment of left superior PV with left atrium (LA): Ablation zone with complete necrosis and edematic loosening of endocardium, subendocardium and thin myocardial layer. Hemorrhaghic pericarditis (P) seen on the epicardial site of L.A. Nervous fibres (N) in the transition zone. B. Magnification from panel A: Multipele nervous fibers in the Subepicardial fatty tissue, some fibers display signs of different degrees of thermal damage (*)

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figuur 1
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figuur 4