Aus dem
CharitéCentrum für Herz-, Kreislauf- und Gefäßmedizin
Klinik für Kardiovaskuläre Chirurgie
Direktor: Prof. Dr. med. W. Konertz

Habilitationsschrift

Die chirurgische Therapie von Vorhofflimmern: Pathophysiologische und klinische Untersuchungen zur Vorhofablation

zur Erlangung der Lehrbefähigung
für das Fach Herzchirurgie

vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité - Universitätsmedizin Berlin

von

Dr. med. Herko Grubitzsch
geboren am 22.01.1970

eingereicht: März 2011

Dekanin: Frau Prof. Dr. med. A. Grüters-Kieslich

1. Gutachter: .....

2. Gutachter: .....

Inhaltsverzeichnis

Abkürzungen

AF-CHF	“Atrial Fibrillation and Congestive Heart Failure“-Sudie
AFFIRM	“Atrial Fibrillation Follow-up Investigation of Rhythm Management”-Studie
AFZL	atriale fibrillatorische Zykluslänge
ΔAFZL	Differenz der atrialen fibrillatorische Zykluslänge
Ca^{2+}	Calciumionen
EKG	Elektrokardiogramm
EuroSCORE	European System for Cardiac Operative Risk Evaluation
fpm	fibrillations per minute
HR	hazard ratio
K^{+}	Kaliumionen
KI	Konfidenzintervall
LVEDD	left ventricular enddiastolic diameter
LVEDP	left ventricular enddiastolic pressure
LVEF	linksventrikuläre Ejektionsfrakltion
MFR	mean fibrillatory rate
MLHF	Minnesota Living with Heart Failure
Na^{+}	Natriumionen
n.s.	nicht signifikant
NYHA	New York Heart Association
OR	odds ratio
PCWP	pulmonary capillary wedge pressure
6MWT	6-minute walk test

1. Einleitung

1.1. Epidemiologie, Bedeutung und Prognose von Vorhofflimmern

Vorhofflimmern ist die häufigste anhaltende Herzrhythmusstörung, an der in den Staaten der Europäischen Union ca. 4,5 Millionen Menschen leiden und deren Prävalenz mit dem Lebensalter zunimmt (1). Letztere beträgt bevölkerungsbezogen, sowohl in Nordamerika als auch in Europa, etwa 0,5% in der sechsten Lebensdekade und erreicht im Alter von mehr als 80 Jahren 10-20% (2, 3).

Obwohl Vorhofflimmern auch isoliert auftritt, ist es sehr oft mit strukturellen Herzerkrankungen assoziiert (4). So entwickeln pro Jahr ca. 5% der Patienten mit Mitralklappenerkrankungen Vorhofflimmern (5). Patienten, bei denen eine operative Koronarrevaskularisation bzw. ein Aortenklappenersatz erforderlich ist, weisen in ca. 1% bzw. 10% Vorhofflimmern auf (6, 7).

Aufgrund des steigenden Lebensalters in den Industrieländern werden herzchirurgische Eingriffe zunehmend im hohen Alter durchgeführt. Im Jahr 2009 waren laut Daten der Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie 11,8% der Patienten älter als 80 Jahre verglichen mit 4,5% im Jahr 2000 (8).

Oft sind Vorhofflimmern und Herzinsuffizienz miteinander vergesellschaftet und verstärken sich gegenseitig (9). So nimmt die Prävalenz von Vorhofflimmern mit dem klinischen Schweregrad der Herzinsuffizienz zu: sie beträgt bei Patienten mit Herzinsuffizienz im Stadium NYHA (New York Heart Association) II ca. 10% und im Stadium NYHA IV ca. 50% (9).

Vorhofflimmern kann mit verschiedenen Symptomen in Erscheinung treten (10). Die Arrhythmie selbst bedingt Herzrasen und den unregelmäßigen Puls. Als Folgen können sich sowohl Schwindel, Schwäche und Luftnot als auch alle Formen von thromboembolischen Ereignissen - vor allem zerebral - manifestieren. Bei einem relevanten Teil der Patienten bzw. Arrhythmieepisoden treten keine Symptome auf. Dennoch resultiert ein hohes Risiko thromboembolischer Komplikationen und eine eingeschränkte Prognose. In großen, epidemiologischen Studien erwies sich Vorhofflimmern als unabhängiger Risikofaktor für das Auftreten von Schlaganfällen, die Entwicklung einer Herzinsuffizienz und vorzeitigen Tod (11-13). Auch bei Patienten, die sich einer koronaren Bypass-Operation unterzogen, führte bereits präoperativ

bestehendes Vorhofflimmern mit einer 10-Jahres-Überlebensrate von 42% (66% ohne Vorhofflimmern) zu einer deutlichen Reduktion der Langzeitprognose (6).

1.2. Pathophysiologie des Vorhofflimmerns

1.2.1. Trigger und Substrat

Verallgemeinernd sind von den komplexen elektrophysiologischen Grundlagen des Vorhofflimmerns zwei wesentliche Faktoren für das Auftreten und die Aufrechterhaltung dieser Rhythmusstörung verantwortlich: der auslösende Trigger und das die Arrhythmie stabilisierende Substrat (14). Als Trigger kommen viele Mechanismen in Frage, die durch abnormale Impulsbildung zu fokal ektopischen Arrhythmie-Generatoren führen (15). Am häufigsten stellen atriale Extrasystolen, die im Bereich der Mündung der Pulmonalvenen in den linken Vorhof entstehen, diese Trigger dar (16, 17). Zur Aufrechterhaltung von Vorhofflimmern müssen sich atrial kreisende Erregungen (Macro-Reentry) bilden, für die Bedingungen wie Verkürzung der Refraktärzeit, Abnahme der Leitungsgeschwindigkeit, Inhomogenitäten der Erregungsausbreitung und Vorhofdilatation das Substrat darstellen.

1.2.2. Atriales Remodeling

Zeitabhängig induziert Vorhofflimmern auf elektrophysiologischer, kontraktiler und struktureller Ebene Veränderungen am Vorhofmyokard. Diese werden zusammenfassend als atriales Remodeling bezeichnet und bedingen scheinbar die typische Progression der Arrhythmie (18). Neben der verkürzten atrialen Refraktarität und reduzierter Leitungsgeschwindigkeit ist ein Anstieg der atrialen Fibrillationsfrequenz, die vom Oberflächen-EKG bestimmt werden kann, charakteristisch für das elektrische Remodeling (18, 19). Die Abnahme bzw. der Verlust der atrialen Kontraktilität ist der Hauptbefund des kontraktilen Remodeling (18). Auf zellulärem Niveau umfassen die durch Vorhofflimmern induzierten strukturellen Veränderungen eine Zunahme der Zellgröße, die Akkumulation von Glykogen, den Verlust von Sarcomeren, eine veränderte Connexin-Expression, die Fragmentierung des sarcoplasmatischen

Retikulums etc., während makroskopisch die atriale Dilatation dem strukturellen Remodeling entspricht (18).
Mit Berichten über eine verminderte atriale Kontraktilität bei Patienten mit Vorhofflimmern, die sich einem herzchirurgischen Eingriff unterzogen oder über die prädiktive Rolle der atrialen Fibrillationsfrequenz für die Sinusrhythmus-Konversion nach pharmakologischer Behandlung, rückte die Analyse des atrialen Remodeling in den Fokus der klinischen Medizin (20-22). Es wurde postuliert, dass die individuelle Quantifizierung des Remodeling-Prozesses zur Vorhersage der Therapie-Effektivität nützlich ist (19).

1.2.3. Vorhofflimmern und Herzinsuffizienz

Der Zusammenhang zwischen Vorhofflimmern und Herzinsuffizienz beruht aus pathophysiologischer Sicht auf einer wechselseitigen Verstärkung (9). Zum einen begünstigt die Herzinsuffizienz Vorhofflimmern, da die hämodynamische Überlast und die spezifische neuro-endokrine Stimulation Änderungen der atrialen elektrophysiologischen Charakteristika provozieren. Zum anderen kann Vorhofflimmern eine Herzinsuffizienz hervorbringen, da der Verlust der atrialen Kontraktion und die irreguläre ventrikuläre Antwort das Schlagvolumen reduzieren und die Tachykardie eine Kardiomyopathie induzieren kann. Klinische Daten legen nahe, dass Patienten bei denen eine Herzinsuffizienz von Vorhofflimmern begleitet wird, eine schlechte Prognose haben. Sowohl die Letalität (Gesamtletalität, plötzlicher Tod und Pumpversagen) als auch die Morbidität (Hospitalisierung) erwies sich bei Patienten mit Herzinsuffizienz und Vorhofflimmern als signifikant erhöht (23-25).

1.3. Klassifikation

Die führenden amerikanischen und europäischen Fachgesellschaften unterteilen im Wesentlichen paroxysmales, persistierendes und permanentes Vorhofflimmern (1). Danach gilt Vorhofflimmern als paroxysmal, wenn es innerhalb von 7 Tagen spontan endet, als persistierend, wenn es länger als 7 Tage besteht und durch pharmakologische oder elektrische Kardioversion beendet werden kann und als

permanent, wenn eine Kardioversion erfolglos war oder nicht durchgeführt bzw. darauf verzichtet wurde. Da sowohl die klinische Manifestation als auch die Wahl der adäquaten Intervention von den zugrundeliegenden elektrophysiologischen Veränderungen bestimmt wird, wurde von Cox (26) eine vereinfachende Klassifikation vorgeschlagen (Tabelle 1): Tritt Vorhofflimmern immer wieder vorübergehend auf, so steht elektrophysiologisch ein Trigger im Vordergrund und es wird als intermittierend klassifiziert. Ist Vorhofflimmern immer präsent, d.h. die atrialen Macro-Reentry-Kreise erhalten sich ohne Notwendigkeit eines Triggers selbst aufrecht, wird es als kontinuierlich klassifiziert.

AHA/ACC/ECS-Klassifikation	elektrophysiologische Grundlage	Cox-Klassifikation
Paroxysmal	fokale Trigger	intermittierend
persistierend permanent	Makro-Reentry-Kreise	kontinuierlich

Tabelle 1: Klassifikationen von Vorhofflimmern und ihr elektrophysiologischer Bezug (1, 26)

1.4. Gegenstand, Ziele und Fragestellungen der Untersuchungen

Anfänglich wurde von Cox und Mitarbeitern die Maze-Operation als chirurgische Therapie von Vorhofflimmern entwickelt (27). Bei diesem Eingriff werden durch Schaffung multipler atrialer Inzisionen Narben erzeugt, die Reentry-Kreise unterbrechen bzw. Herde ektoper Aktivität isolieren. Trotz hoher Effektivität wurde diese Prozedur aufgrund ihrer Komplexität und des operativen Aufwands nur in wenigen Kliniken etabliert (28, 29). Mit der Entwicklung verschiedener Technologien zur Erzeugung linienförmiger, atrialer Narben ohne Unterbrechung der Gewebsintegrität konnte sich die chirurgische Behandlung des Vorhofflimmerns vor allem als begleitende Therapie bei

herzchirurgischen Eingriffen in den letzten Jahren weit verbreiten und eine hohe Erfolgsrate erreichen (30-36). Dennoch kann Vorhofflimmern fortbestehen oder im Verlauf wieder auftreten (29, 33, 34, 37).

In den nachfolgenden Arbeiten wurden klinische und pathophysiologische Faktoren (elektrisches, kontraktiles und strukturelles Remodeling) hinsichtlich ihres prädiktiven Werts für die Behandlungsergebnisse analysiert sowie das Operationsverfahren als Bestandteil der Herzinsuffizienztherapie evaluiert. Die vorliegenden Untersuchungen umfassten folgende Schwerpunkte:

1. Evaluation eines neuen hochauflösenden Oberflächen-EKG zur Bestimmung der atrialen Fibrillationsfrequenz als Parameter des elektrischen Remodeling
2. Die Analyse der Rolle des elektrischen, kontraktilen und strukturellen Remodeling für die Ergebnisse nach chirurgischer Ablation von Vorhofflimmern
3. Die Analyse klinischer Parameter für die Ergebnisse nach chirurgischer Ablation
4. Welche Bedeutung hat die chirurgische Ablation von Vorhofflimmern für Patienten mit chronischer Herzinsuffizienz

2. Eigene Arbeiten

2.1. Untersuchung des atrialen Remodeling

Mit der Bestimmung der Kontraktionskraft atrialer Myokardstreifen und der Echokardiografie waren Methoden zur patientenindividuellen Analyse des atrialen Remodeling auf kontraktiler und struktureller Ebene in der Klinik etabliert. Zur Untersuchung des elektrischen Remodeling wurde ein neues EKG-System (CardioLink®, getemed AG, Teltow, Deutschland) evaluiert. Nachdem die Analyse der fibrillatorischen Aktivität aus dem Oberflächen-EKG entwickelt worden war (38, 39), blieben die Algorithmen zur Extraktion des Fibrillationssignals und die anschließende Fourier-Analyse zunächst nur diesen speziellen Laboratorien vorbehalten. Mit dem CardioLink®-System wurde ein EKG-Gerät verfügbar, das sich durch eine hochverstärkte, hochauflösende EKG-Aufzeichnung mit nachfolgender Signalverarbeitung zur nicht-invasiven Bestimmung der atrialen fibrillatorischen Aktivität, einschließlich abgeleiteter Parameter wie der atrialen fibrillatorischen Zykluslänge (AFZL), auszeichnet.

2.1.1. Analyse der atrialen fibrillatorischen Aktivität

Grubitzsch H, Modersohn D, Leuthold T, Konertz W.
Analysis of atrial fibrillatory activity from high-resolution surface electrocardiograms: Evaluation and application of a new system.
Exp Clin Cardiol. 2008; 13: 29-35.

Zusammenfassung der Ergebnisse

Zur Frequenzanalyse des atrialen Signals von Oberflächenpotentialen erwiesen sich die Ableitungen V_1, V_2 und II am geeignetsten. Die mittlere Fibrillationsfrequenz (mean fibrillatory rate, MFR) in V_1 korrelierte signifikant mit der in V_2 ($r=0,98$; $p<0,05$) und II ($r=0,88$; $p<0,05$). Die Frequenzspektren in V_1 ($n=27$) waren im zeitlichen Verlauf (13,6±3,8 Minuten) hinsichtlich der Verteilung und Konfiguration der maximalen

Frequenzkomponente und abgeleiteter Parameter stabil. Intraoperative Messungen (n=9) zeigten keine Beeinflussung der fibrillatorischen Aktivität durch Allgemeinnarkose. Im rechten Herzohr, im rechten Vorhof, im linken Vorhof und im linken Herzohr war der relative Unterschied der MFR bzw. ΔAFZL (Differenz der atrialen fibrillatorischen Zykluslänge) verglichen mit der Oberflächenableitung V_1 mit 5,6%, 6,6%, 6,8% bzw. 5,7% gering. Die MFR variierte zwar zwischen den Patienten, unterschied sich aber an den einzelnen atrialen Lokalisationen innerhalb individueller Patienten nicht. Bei Patienten mit hoher fibrillatorischer Aktivität (>390 fpm [fibrillation per minute], n=25) war eine signifikant schmalere spektrale Breite bei 75% der maximalen Signalamplitude zu beobachten (14±7,6 versus 22±13,3 fpm, $p<0,05$) und es bestand ein nicht-signifikanter Trend zu längerer Dauer des Vorhofflimmerns.

Es wurde gezeigt, dass Parameter der atrialen fibrillatorischen Aktivität mit dem CardioLink®-EKG-System zuverlässig von Oberflächenpotentialen gewonnen werden können und diese mit epikardialen Potentialen übereinstimmen. Somit gestattet dieses System die nicht-invasive Untersuchung des individuellen elektrischen Remodeling.

Analysis of atrial fibrillatory activity from high-resolution surface electrocardiograms: Evaluation and application of a new system

Herko Grubitzsch MD[1], Diethelm Modersohn MD PhD[1], Thomas Leuthold MD[2], Wolfgang Konertz MD PhD[1]

H Grubitzsch, D Modersohn, T Leuthold, W Konertz. Analysis of atrial fibrillatory activity from high-resolution surface electrocardiograms: Evaluation and application of a new system. Exp Clin Cardiol 2008;13(1):29-35.

BACKGROUND: Algorithms of signal processing allow the estimation of atrial fibrillation (AF) activity from surface electrocardiograms (ECGs).
OBJECTIVE: To evaluate a new commercially available ECG system for AF analysis from surface potentials.
METHODS: Patients (n=52, mean [± SD] age of 68±9.6 years) with persistent AF (mean duration 44±52.2 months), referred for cardiac surgery, underwent high-gain, high-resolution ECG preoperatively. After QRST cancellation, the frequency content of AF was identified by fast Fourier transformation. Epicardial potentials were registered at the right atrial appendage, the right atrium (RA), the left atrium (LA) and the left atrial appendage intraoperatively (nine patients).
RESULTS: Mean (± SD) fibrillatory rate (MFR) in lead V_1 (393±40.4 fibrillations/min [fpm]) correlated significantly with V_2 (391±43.3 fpm, r=0.976; P<0.05) and II (379±41.1 fpm, r=0.878; P<0.05), and was stable within an interval of 13.6±3.8 min (27 patients). In the right atrial appendage, RA, LA and left atrial appendage, the relative difference in MFR was small (5.6%, 6.6%, 6.8% and 5.7%, respectively, compared with V_1). The mean peak frequency component at 75% of the maximum power was significantly smaller in the LA than in the RA (13±4.2 fpm versus 22±7.2 fpm, respectively; P<0.01), and in patients with high (more than 390 fpm) compared with low (390 fpm or fewer) fibrillatory activity (14±7.6 fpm versus 22±13.3 fpm, respectively; P<0.05). There was a nonsignificant trend to higher fibrillatory activity with longer AF duration. Other characteristics (age, sex, LA size, ejection fraction, type of heart disease and medication) were not associated with the MFR.
CONCLUSIONS: Using the CardioLink system, AF analysis from surface ECG is reliable and equivalent to epicardial measurements. By noninvasive assessment of individual electrical remodelling, this system certainly supports clinical AF research.

Key Words: *Ablation; Atrial fibrillation; Frequency analysis; Surface ECG*

Atrial fibrillation (AF), the most frequent sustained atrial arrhythmia, affects approximately 1% of the population, with increasing incidence in elderly people, and is associated with significant morbidity (1,2). During the past decade, new treatment options for AF patients have been introduced, including catheter-based and surgical techniques for atrial ablation (3,4). Although the results of these approaches are very promising, factors influencing the success rate and long-term outcome are incompletely understood.

Today, it is known that the progressive nature of AF results from electrical, contractile and structural remodelling of the atria, which is induced by the underlying heart disease and the arrhythmia itself (5). Because of a great variety of potential interactions, AF is not a homogenous arrhythmia. Consequently, clinical AF research should be focused on the characterization of remodelling in individual patients.

For quantification of atrial electrical remodelling, analysis of fibrillatory activity from surface electrocardiograms (ECGs) has been developed (6-9). Fibrillatory rate and derived parameters – including atrial fibrillatory cycle length (AFCL) – determined using this method exhibited a marked interindividual variability but agreed with values obtained from intra-atrial recordings (7,10,11).

Until recently, algorithms extracting the fibrillatory baseline signal and subsequent Fourier transform have not been implemented in commercially available ECG systems. With the new CardioLink system (getemed AG, Germany), ECG equipment is now on the market featuring high-gain, high-resolution ECG recording and consecutive signal processing for noninvasive assessment of atrial fibrillatory activity.

The purposes of the present study were to evaluate the CardioLink system and to investigate atrial fibrillatory activity in clinical cases of chronic AF.

PATIENTS AND METHODS

Study population

After giving informed consent, the patients (n=52) who were referred to our department for surgical treatment of mitral valve disease, aortic valve disease, coronary artery disease or combined heart disease were studied. Table 1 summarizes the demographic data of the patients. According to the established definitions, all patients presented persistent or continuous AF (12,13). Patients with paroxysmal AF and patients on class I or class III antiarrhythmic drugs were excluded. The study protocol was constructed in accordance with the Declaration of Helsinki and approved by a local ethics committee. All

[1]*Department of Cardiovascular Surgery, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, Berlin;* [2]*Getemed AG, Teltow, Germany*
Correspondence: Dr Herko Grubitzsch, Klinik für Kardiovaskuläre Chirurgie, Charité – Universitätsmedizin Berlin, Campus Charité Mitte, Charité-Platz 1, 10117 Berlin, Germany. Telephone 0049-0-30-450522092, fax 0049-0-30-450522921, e-mail herko.grubitzsch@charite.de
Received for publication June 18, 2007. Accepted September 3, 2007

TABLE 1
Patient characteristics

Characteristic	n (%)	Mean ± SD	Range
Age, years		68±9.6	40–88
Male patients	22 (42.3)		
Body surface area, m^2		1.8±0.24	1.5–2.3
New York Heart Association class		2.8±0.81	II–IV
Previous embolism	1 (1.9)		
Atrial fibrillation duration, months		44±52.2	1–252
Left atrial diameter, mm		50±8.9	32–64
Left ventricular ejection fraction		0.51±0.116	0.20–0.73
Left ventricular end-diastolic diameter, mm		53±6.5	35–68
Coronary artery disease	15 (28.8)		
3-vessel disease	11 (73.3)		
Previous myocardial infarction	9 (60.0)		
Mitral valve disease	15 (28.8)		
Aortic valve disease	7 (13.5)		
Combined heart disease	15 (28.8)		
Arterial hypertension	37 (71.2)		
Pulmonary hypertension	25 (48.1)		
Diabetes	18 (34.6)		
Chronic obstructive pulmonary disease	9 (17.3)		
Renal dysfunction	12 (23.1)		
Arteriopathy (noncardiac)	11 (21.2)		
Beta-blocker	38 (73.1)		
Digitalis	24 (46.2)		
Calcium channel blocker	5 (9.6)		

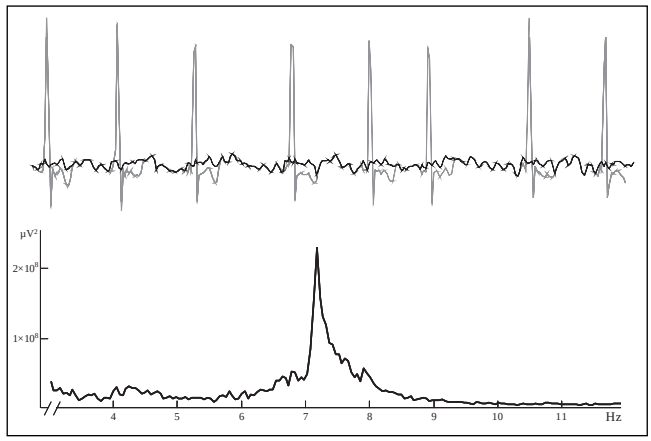

Figure 1) *Signal processing. The* **top** *graph shows the original ECG signal (grey line), recorded from a patient with atrial fibrillation, and the extracted atrial signal (black line) after QRST cancellation. This fibrillatory signal was then subjected to Fourier transform. In the* **bottom** *graph, the resulting spectral profile of a 5 min ECG is depicted in the 3 Hz to 12 Hz (180 to 720 fibrillations/min) range, which reveals a unimodal peak distribution*

patients underwent concomitant AF ablation, but analysis of procedural outcome was outside the scope of the present study.

Subgroups of patients were used to evaluate the ECG system. In the first 23 patients (subgroup 1), the quality of the atrial signal, as well as the generated power spectrum, was analyzed in each lead to determine the most suitable leads for frequency analysis from surface potentials. In 27 patients (subgroup 2), temporal stability of the mean fibrillatory rate (MFR) was investigated. During surgery, the influence of general anesthesia was investigated (subgroup 3), and surface and epicardial ECG analysis was compared in nine patients (subgroup 4).

Surface ECG

Each patient, laying relaxed in a supine position after a 5 min equilibration period, underwent a high-gain, high-resolution surface ECG (CardioLink) using 12 standard leads. Recordings lasted at least 5 min. For studying temporal stability of fibrillatory activity, ECG was recorded for up to 28 min in 27 patients.

Epicardial ECG

After giving additional informed consent, a subgroup of nine patients underwent intraoperative ECG recordings. Surface ECG was repeated after induction of anesthesia and before skin incision. For general anesthesia, fentanyl, midazolam, isoflurane and pancuronium were used. Epicardial atrial signals were obtained before starting extracorporeal circulation. After sternotomy, the pericardium was opened and temporary electrodes (TME 67 TL bifurcated, Dr Osypka Medizintechnik GmbH, Germany) were sutured to the right atrial appendage (RAA), the right atrium (RA) (ie, the free wall near the interatrial septum), the roof of the left atrium (LA) and the left atrial appendage (LAA). Unipolar electrodes were referenced to the Wilson central terminal. Recording time was 5 min to 10 min.

Signal processing and analysis

The ECGs were digitized with a sampling rate of 1024 Hz and a 12-bit resolution, resulting in an amplitude resolution of 2.44 μV. Because the ECG system consists of a recorder and personal computer, data were immediately transferred via universal serial bus and stored for later analysis. For isolating atrial activity, an average beat subtraction-based method for QRST cancellation was developed. After low- and high-pass filtering for reduction of noise, muscle artifacts and baseline drifts, QRST detection was performed. In contrast to techniques described previously (14), detected QRST complexes were classified into morphological classes using a cross-correlation technique. For each class, an average beat template was calculated. After temporal and amplitudinal alignment, each template was subtracted from the original QRST complex. The resulting atrial ECG (Figure 1) was downsampled to 50 Hz based on the observation that the frequency content of the atrial signal does not exceed 25 Hz. Spectral analysis was performed by fast Fourier transform. The power spectral density was calculated using the modified periodogram according to Welch (15). A Hamming window of 1024 samples and an overlapping of 512 samples were used. The resulting power spectrum was analyzed in the 3 Hz to 12 Hz (180 fibrillations/min [fpm] to 720 fpm) range (Figure 1). The distribution was regarded as unimodal if one peak frequency component was present, and multimodal if two or more peaks with at least 50% of the maximum amplitude were present (7). As suggested by Bollmann et al (16,17), the peak frequency component was expressed as atrial MFR as fpm. It reflects the mean fibrillatory frequency and can be converted to the dominant AFCL (cycle length = 1/frequency; 1 [fbm] = 1 fibrillation/60,000 ms).

TABLE 2
Characteristics of signal quality

Lead	Absolute amplitude of the atrial signal, mV (mean ± SD)	Relative amplitude of the atrial signal*, %	Adequate frequency spectrum, %	Frequency spectrum not usable, %	Total power of the spectral signal, $\mu V^2/Hz$ (mean ± SD)	Unimodal spectrum†, %	Multimodal spectrum†, %	Power of mean peak frequency‡, μV^2 (mean ± SD)
I	0.04±0.014	7.0	86.9	13.1	255±219.4	53.3	46.7	$0.5\times10^8\pm0.41\times10^8$
II	0.04±0.012	7.3	100.0	0.0	494±421.5	72.2	27.8	$1.0\times10^8\pm0.68\times10^8$
III	0.04±0.012	10.3	91.3	8.7	387±238.4	86.7	13.3	$1.2\times10^8\pm1.12\times10^8$
aVR	0.04±0.016	9.0	73.9	26.1	257±215.1	69.2	30.8	$0.5\times10^8\pm0.41\times10^8$
aVL	0.03±0.018	11.0	86.9	13.1	230±176.2	86.7	13.3	$0.5\times10^8\pm0.47\times10^8$
aVF	0.04±0.013	10.0	91.1	8.9	379±308.6	85.7	14.3	$0.9\times10^8\pm0.78\times10^8$
V_1	0.05±0.018	7.9	100.0	0.0	774±708.3	100.0	0.0	$2.1\times10^8\pm1.80\times10^8$
V_2	0.05±0.019	6.2	73.9	26.1	571±371.1	100.0	0.0	$1.4\times10^8\pm1.20\times10^8$
V_3	0.07±0.028	7.1	69.6	30.4	1140±614.7	66.7	33.3	$2.9\times10^8\pm1.94\times10^8$
V_4	0.07±0.038	6.9	60.9	39.1	678±322.0	25.0	75.0	$0.6\times10^8\pm0.23\times10^8$
V_5	0.06±0.024	5.6	65.2	34.8	641±306.3	37.5	62.5	$0.8\times10^8\pm0.50\times10^8$
V_6	0.05±0.023	5.0	65.2	34.8	534±362.5	55.5	44.5	$1.0\times10^8\pm0.97\times10^8$

*Signal characteristics were analyzed in the first 23 patients (11 men, 12 women). Regarding age, duration of atrial fibrillation and left atrial diameter, this cohort was not different from the whole study population. *Percentages are relative values and refers to the R wave; †To estimate the distribution of the power spectrum, only adequate frequency spectra were analyzed; ‡To determine the power of the mean peak frequency, only unimodal spectra were analyzed*

Assessment of signal quality and the peak frequency component

In the first 23 patients, the absolute amplitudes of the atrial potentials were obtained by measuring 10 fibrillation waves. The relative amplitude of the atrial signal is given as a percentage of the relative amplitude estimated in 10 beats. The quality of the spectrum resulting from Fourier transformation was classified as adequate if unimodal or multimodal peaks were detectable, or as unusable if no peak was detectable. The total power of the spectral signal and the power maximum of the peak frequency component were determined. For characterizing the peak frequency component, unimodal peaks in lead V_1 were analyzed. To quantify the magnitude of the peak frequency component, the power density within 30 fpm of the peak frequency was related to the power density of the total signal in the 3 Hz to 12 Hz range. The spectral width (SW) of the peak was determined as the difference in fibrillatory rate at 90% (SW 90) and 75% (SW 75) of the maximum power of peak frequency, respectively.

Analysis of MFR variability

MFR and peak characterizing parameters were investigated preoperatively in different surface leads (subgroup I) and at different times (subgroup II), as well as intraoperatively under general anesthesia (subgroup III) and at different atrial sites (subgroup IV). Multimodal spectra were excluded from evaluation.

Atrial fibrillatory activity and clinical characteristics

According to the median of the observed MFR distribution, the whole study population was divided into patients with low fibrillatory activity (group A) and patients with high fibrillatory activity (group B). Differences in the parameters of fibrillatory activity, such as SW 75 and the ratio of SW 90/SW 75, as well as the main clinical determinants like age, sex, heart rate, LA size, left ventricular ejection fraction (LVEF), AF duration, type of disease and medication, were analyzed in these groups. All patients underwent transthoracic echocardiographic examination using the HP Sonos 5500 (Hewlett Packard, USA). Left atrial and left ventricular diameters were measured using standard techniques. LVEF was assessed by the Simpson method.

Statistical analysis

Unless otherwise indicated, data are presented as the mean ± SD, or as absolute and relative frequencies. To examine variability of the peak frequency component and its derived parameters in different leads, unpaired Student's *t* test was used after testing for a normal distribution. For analyzing time dependency of these data, paired Student's *t* test was applied. To describe the relation of MFR between different leads, Pearson's correlation coefficient was calculated. Univariate analyses were performed to identify factors associated with high or low fibrillatory activity using the unpaired, two-tailed Student's *t* test for continuous variables and the χ^2 test for categorical variables. A value of $P<0.05$ was considered to be significant. Statistical analysis was performed using a statistical software program (SPSS 13.0 for Windows, SPSS Inc, USA).

RESULTS

Extraction of atrial fibrillatory activity from the surface ECG

Signal characteristics, obtained by analyzing the extracted atrial potentials and the generated power spectrum in every single lead from the first 23 patients (11 men, 12 women), are summarized in Table 2. Regarding age, duration of AF and left atrial diameter, these patients were not different from the whole study population. The most suitable leads for frequency analysis from surface potentials were V_1, V_2 and II. All frequency spectra obtained from V_1 and II were adequate. Adequate spectra from V_1 and V_2 were always characterized by unimodal peak detection. In lead II, a multimodal frequency distribution was observed in five of 18 patients (27.8%). Regarding multiple peaks (in up to 75% in V_4), no patient exhibited that distribution in each lead. Although the highest amplitudes of atrial potentials and the highest total power of the frequency

TABLE 3
Mean fibrillatory rate (MFR) in different leads

	Lead		
	V_1	V_2	II
n	50	39	43
MFR, fpm	393±39.8	392±40.8*	379±40.4*
Range, fpm	288–468	288–468	300–480
Dominant AFCL, ms	154±16.8	155±17.6*	160±17.1*
Range, ms	128–208	128–208	125–200
SW 90, fpm	8±7.9	10±11.9*	9±8.5*
Range, fpm	3–35	3–56	3–44
SW 75, fpm	18±12.7	23±18.1*	21±15.4*
Range, fpm	3–53	3–76	3–53

*Data are presented as the mean ± SD unless otherwise indicated. *Not significant compared with V_1. AFCL Atrial fibrillation cycle length; fpm Fibrillations/min; NS Not significant; SW 75 Spectral width of the peak at 75% of the maximum power of peak frequency; SW 90 Spectral width of the peak at 90% of the maximum power of peak frequency*

TABLE 4
Temporal stability of mean fibrillatory rate

	Time 1 (mean ± SD)	Time 2 (mean ± SD)	P
Mean fibrillatory rate, fpm	400±51.2	398±49.4	NS
Dominant AFCL, ms	153±22.1	153±22.3	NS
Power of peak frequency, μV^2	$1.9\times10^8\pm1.72\times10^8$	$2.2\times10^8\pm2.65\times10^8$	NS
SW 90, fpm	8±7.5	9±11.5	NS
SW 75, fpm	20±14.6	20±15.4	NS
SW 90/SW 75 ×100, %	43±18.0	48±25.1	NS

In 27 patients (14 men, 13 women), frequency spectra in V_1 were analyzed before (time 1) and after (time 2) an interval of 13.6±3.8 min. AFCL Atrial fibrillation cycle length; fpm Fibrillations/min; NS Not significant; SW 75 Spectral width of the peak at 75% of the maximum power of peak frequency; SW 90 Spectral width of the peak at 90% of the maximum power of peak frequency; SW 90/SW 75 Ratio of spectral width of the peak at 90% and 75% of the maximum power of peak frequency in per cent

spectra were detected in chest wall leads, frequency spectra were not usable in approximately one-third of leads V_3 to V_6. In these cases, no relation to patient characteristics, such as weight and body surface area, or magnitude of atrial potentials was found. Power density within 30 beats/min of the MFR was 260±215.7 μV^2/Hz in unimodal peaks in V_1, ie, 34.8% of the total spectral signal in the 3 Hz to 12 Hz range, which contained a power density of 774±708.3 μV^2/Hz. The SW 90 and SW 75 were 6±4.8 fpm and 16±10.0 fpm, respectively, indicating a relatively distinct atrial fibrillatory rate.

Stability of atrial fibrillatory activity

Within the total study population, frequency analysis from surface ECGs failed completely in two of the 52 patients (3.9%) because of low signal amplitude of the atrial potentials after QRST cancellation. In leads V_2 and II, frequency spectra were not usable in 11 and seven patients, respectively. A comparison of adequate spectra from leads V_1, V_2 and II is shown in Table 3. Related to lead V_1, MFR and SW (either SW 90 or SW 75) did not significantly differ in leads V_2 and II. There was a strong correlation of dominant rate between V_1 and V_2 (r=0.976; P<0.05), as well as between V_1 and II (r=0.874; P<0.05). Rate dispersion between V_1 and V_2, and between V_1 and II, measured 6±7.3 fpm (range 0 fpm to 24 fpm) and 17±14.1 fpm (range 0 fpm to 60 fpm), respectively. In 27 patients (14 men, 13 women), frequency spectra in V_1 were analyzed before and after an interval of 13.6±3.8 min. Table 4 shows no differences in distribution and configuration of peak frequency component and derived parameters. In patients undergoing intraoperative measurements (n=9), general anesthesia did not influence fibrillatory activity (MFR 368±35.3 fpm, SW 75 29±9.6 fpm) compared with preoperatively determined parameters (MFR 377±39.9 fpm, P not significant; SW 75 24±17.5 fpm, P not significant).

TABLE 5
Fibrillatory activity from surface and epicardial electrocardiograms (ECGs)

		Surface ECG (V_1)	Epicardial ECG			
Patient	Factor	Intraoperative	RAA	RA	LA	LAA
1	AFCL, ms	159	161	159	156	–
	SW 75, fpm	32.2	20.5	35.1	11.7	–
2	AFCL, ms	180	–	–	194	182
	SW 75, fpm	38.0	–	–	17.5	17.5
3	AFCL, ms	170	164	172	170	–
	SW 75, fpm	32.2	17.5	20.5	14.6	–
4	AFCL, ms	154	172	168	159	168
	SW 75, fpm	17.5	14.6	11.7	8.8	11.7
5	AFCL, ms	154	–	170	186	180
	SW 75, fpm	20.5	–	17.5	14.6	20.5
6	AFCL, ms	185	191	205	182	182
	SW 75, fpm	26.3	26.3	32.2	8.8	14.6
7	AFCL, ms	164	168	170	182	167
	SW 75, fpm	23.4	20.5	20.5	5.8	11.7
8	AFCL, ms	147	152	152	159	156
	SW 75, fpm	14.6	11.7	35.1	5.8	11.7
9	AFCL, ms	179	185	194	191	170
	SW 75, fpm	26.3	23.4	20.5	17.5	8.8

Results of intraoperative ECG recordings in a subgroup of nine patients. AFCL Atrial fibrillation cycle length; fpm Fibrillations/min; LA Left atrium; LAA Left atrial appendage; RA Right atrium; RAA Right atrial appendage; SW 75 Spectral width of the peak at 75% of the maximum power of peak frequency

Local atrial fibrillatory activity

For epicardial ECG, the LAA could not be reached for safe electrode placement in two of nine cases. Because of electrical artifacts, frequency spectra were inadequate in ECG from two RAA and one RA site. Atrial fibrillatory activity measured directly at the atria is shown in Table 5. The respective difference of MFR and AFCL to intraoperative surface ECG (V_1) was small, with relative values of 5.6%, 6.6%, 6.8% and 5.7% in the RAA, RA, LA and LAA, respectively. As demonstrated in Figure 2, the atrial MFR varied from 282 fpm to 396 fpm among patients, but was quite stable at different atrial sites within individual patients. Regarding SW 75, atrial fibrillatory activity was found to be more distinct in the LA than in the RA (13±4.2 fpm versus 22±7.2 fpm; P<0.01).

Atrial fibrillatory activity and clinical characteristics

Statistical analysis of MFR demonstrated normal distribution within the study population (393±39.8 fpm, median 390 fpm, range 288 fpm to 468 fpm). For further investigation of atrial

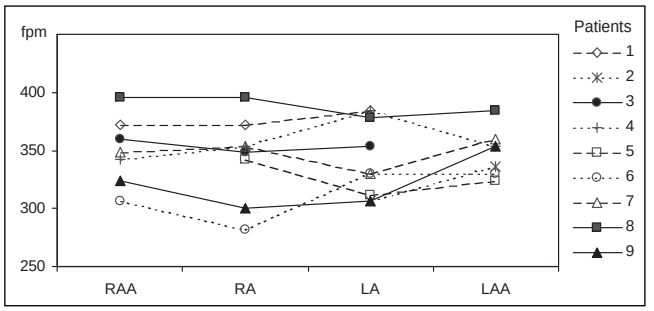

Figure 2) *Mean fibrillatory rate at different atrial sites. The mean fibrillatory rate analyzed in nine patients at different atrial sites demonstrated intraindividual stability. fpm Fibrillations/min; LA Left atrium; LAA Left atrial appendage; RA Right atrium; RAA Right atrial appendage*

fibrillatory activity and its potential relations to clinical characteristics, the study cohort was analyzed according to low fibrillatory activity (group A, 390 fpm or less, n=25) and high fibrillatory activity (group B, more than 390 fpm, n=25). Table 6 demonstrates that the SW 75 was significantly smaller in patients with higher fibrillatory activity. There was a non-significant trend to longer AF duration in group B. However, there was no difference between the two groups in heart rate, age, sex, LA size, LVEF, underlying heart disease or medication (beta-blocker).

TABLE 6
Comparison of patients with low (group A) and high (group B) atrial fibrillatory activity

	Group A (n=25)	Group B (n=25)	P
Dominant AFCL,ms	166±14.4	142±7.5	<0.001
SW 75, fpm	22±13.3	14±7.6	0.032
SW 90/SW 75, %	52±26.2	42±20.6	NS
Heart rate, beats/min	77±20.6	80±13.2	NS
Age, years	70±10.8	67±6.6	NS
Male patients, n (%)	9 (36)	10 (40)	NS
Atrial fibrillation duration, months	42±50.3	49±59.3	NS
Left atrial diameter, mm	50±9.5	49±8.7	NS
Left ventricular ejection fraction, %	51±13.1	52±10.0	NS
Underlying disease, n (%)			
Valvular heart disease	12 (48)	10 (40)	NS
Coronary artery disease	8 (32)	7 (28)	NS
Combined	5 (20)	8 (32)	NS
Medication (beta-blocker), n (%)	20 (80)	16 (64)	NS

Data are presented as the mean ± SD unless otherwise indicated. AFCL Atrial fibrillation cycle length; fpm Fibrillations/min; NS Not significant; SW 75 Spectral width of the peak at 75% of the maximum power of peak frequency; SW 90 Spectral width of the peak at 90% of the maximum power of peak frequency; SW 90/SW 75 Ratio of spectral width of the peak at 90% and 75% of the maximum power of peak frequency in per cent

DISCUSSION

It has been demonstrated previously that atrial fibrillatory activity can be extracted by frequency analysis of the atrial component in surface ECGs from patients with AF (6). This method was found to accurately reflect the average rate of AF directly recorded from endocardium (7,10,11). However, all of these computer-based algorithms for signal processing and analysis have been developed in specialized laboratories (6-8,16) and have not been made commercially available. Recently, the new CardioLink ECG system, featuring a high-gain, high-resolution ECG recorder, as well as software for signal processing and frequency analysis, was introduced into the market. By evaluating this equipment, we demonstrated its usefulness in a routine clinical setting. We found a significantly smaller configuration of the peak frequency component with higher fibrillatory activity. Furthermore, a smaller peak was observed in the LA. There was a trend to higher fibrillatory activity with longer AF duration. Other clinical characteristics were not associated with atrial fibrillatory activity.

AF analysis from surface ECG

We found V_1, V_2 and II to be the most suitable leads for frequency analysis from surface potentials. Because atrium lead distance increases from V_2 to V_6, it is understandable why spectral analysis often fails in leads V_3 to V_6. In some patients, we observed multimodal (mostly bimodal) frequency distributions. Assuming this pattern reflects atrial activity, it may be due to spatial or temporal difference in fibrillatory rate (7). However, there were no patients who exhibited this distribution in all leads; it was not found especially in V_1 and V_2. Moreover, the second peak was almost always approximately 4 Hz (240 fpm), suggesting that it may represent a method associated with an artifact rather than real atrial activity.

Together with previous studies (7,16), the present study has demonstrated an excellent correlation of atrial fibrillatory activity among different leads with different vectors (Table 3). As with other studies (6,7,9,16), we often found single and narrow-banded frequency spectra when applying the described Fourier analysis. This particular configuration, characterizing a relatively distinct MFR, appeared in different leads as well. In contrast to a previous study (8), we found no significant variations in the width of the frequency spectrum in different leads.

Sequential measurements by the CardioLink system in 27 patients demonstrated reproducible results in frequency analysis and temporal stability of fibrillatory parameters (Table 4). Holm et al (7) concluded previously that 5 min of ECG recording were sufficient to capture the majority of the temporal dynamics of the AFCL. For enhanced time resolution, a new method, by which a time-varying spectral profile was produced, was developed (18). It may be useful to investigate short-term changes, such as the effects of intravenous antiarrhythmic drugs.

AF activity from epicardial measurements

Local AF activity was well represented in surface ECGs (Table 5). This is in concordance with findings from other studies (7,10,11), demonstrating accurate reflection of AF rate directly recorded from the endocardium in surface potentials. From an anatomical point of view, the RAA is next to V_1 and may contribute predominantly to potentials of that lead (7). However, the rates determined at RA, LA and LAA sites did not significantly differ from the RAA site. Regardless, hidden short-term spatial variability has to be considered, because ECG registration time was 5 min to 10 min. According to the SW 75, our data suggest a more distinct peak configuration in the LA. On the premise that the magnitude of SW may represent atrial rate heterogeneity (7), this finding could be an indication of a more organized activation in the LA.

Variability of fibrillatory activity and its clinical importance
Fibrillatory rate, determined from surface ECGs or obtained from intra-atrial recordings, is characterized by a marked interindividual variability ranging between 240 fpm and 540 fpm, corresponding with an AFCL of 110 ms to 250 ms (6,7,9,19,20). Thus, frequency analysis may serve as a simple means to determine individual quantification of electrical remodelling (16).

Our finding of a smaller SW 75 in group B patients suggests that atrial rate heterogeneity decreases with increasing fibrillatory rate. Recently, Sasaki et al (21) similarly demonstrated a parallel decrease of the mean AFCL and its coefficient of variation. This means that activations with a short AFCL dominate and possibly suppress those with longer AFCL.

Regarding the natural course of AF progression, we found a nonsignificant trend to a higher MFR with longer AF duration. It has previously been shown that patients with persistent AF exhibited a significantly higher fibrillatory frequency than patients with paroxysmal AF (9). Moreover, during follow-up of patients with persistent AF, a significant decrease of the mean AFCL was demonstrated (21). Distribution of AF duration within a wide range may explain why confirmation of a significant association between MFR and AF duration failed in our cohort. In general, one must remember that data of AF duration, obtained from patients or their referring physicians, are often approximations.

We found no influence of general anesthesia on atrial MFR and SW. Because sedation and analgesia per se – as well as each of the above mentioned drugs – depress chronotropic properties of the heart (22), this finding can be interpreted as a relatively autonomous state of chronically fibrillating atria, at least with respect to the MFR. In contrast, there is evidence that SW can serve as a physiological parameter, because a response to carotid sinus massage was shown (23).

With spectral analysis of surface ECGs, monitoring of antiarrhythmic drug effects and identifying patients who are suitable candidates for pharmacological cardioversion are possible (7,9,16,24,25). Furthermore, it has been shown that a high fibrillatory rate (420 fpm or more) is a risk factor of AF recurrence after electrical cardioversion (25). It remains to be investigated whether fibrillatory rate influences results of surgical AF treatment.

Study limitations
A major limitation of our study is that no controlled comparative assessment to other techniques was performed. Thus, the strengths and weaknesses of this new technology could not be elaborated thoroughly. Nonetheless, epicardial measurements confirmed the validity of frequency parameters obtained from surface ECGs.

Although the study reached some conclusions regarding the clinical significance of atrial fibrillatory activity, the data are from a relatively small number of patients. We tolerated a heterogeneous patient population, because the primary aim was the evaluation of the new ECG system in a routine clinical setting. Influences from underlying heart disease or cardioactive medication have to be considered. Although patients on antiarrhythmic drugs were excluded, basic medication (eg, beta-blockers) could have affected atrial fibrillatory activity by modulating the autonomic nervous system. Using the CardioLink, we are now able to address such questions in larger and more precisely defined cohorts of patients.

CONCLUSIONS

This is the first report on the application of the CardioLink ECG system to investigate AF from surface potentials. We have demonstrated that parameters of atrial fibrillatory activity can be reliably obtained, and that frequency analysis from epicardial and surface potentials is equivalent. We found a significantly smaller configuration of the peak frequency component with higher fibrillatory activity. Furthermore, a smaller peak was observed in the LA. By allowing noninvasive, individual assessment of electrical remodelling, this system certainly supports clinical AF research.

REFERENCES

1. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham study. N Engl J Med 1982;306:1018-22.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995;155:469-73.
3. Haïssaguerre M, Jaïs P, Shah DC, et al. Catheter ablation of chronic atrial fibrillation targeting the reinitiating triggers. J Cardiovasc Electrophysiol 2000;11:2-10.
4. Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. Eur J Cardiothorac Surg 2005;27:258-65.
5. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230-46.
6. Slocum J, Sahakian A, Swiryn S. Diagnosis of atrial fibrillation from surface electrocardiograms based on computer-detected atrial activity. J Electrocardiol 1992;25:1-8.
7. Holm M, Pehrson S, Ingemansson M, et al. Non-invasive assessment of the atrial cycle length during atrial fibrillation in man: Introducing, validating and illustrating a new ECG method. Cardiovasc Res 1998;38:69-81.
8. Pehrson S, Holm M, Meurling C, et al. Non-invasive assessment of magnitude and dispersion of atrial cycle length during chronic atrial fibrillation in man. Eur Heart J 1998;19:1836-44.
9. Bollmann A, Sonne K, Esperer HD, Toepffer I, Langberg JJ, Klein HU. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG. Cardiovasc Res 1999;44:60-6.
10. Slocum JE, Ropella KM. Correspondence between the frequency domain characteristics of simultaneous surface and intra-atrial recordings of atrial fibrillation. IEEE Comput Cardiol 1994;21:781-4.
11. Roithinger FX, SippensGroenewegen A, Karch MR, Steiner PR, Ellis WS, Lesh MD. Organized activation during atrial fibrillation in man: Endocardial and electrocardiographic manifestations. J Cardiovasc Electrophysiol 1998;9:451-61.
12. Lévy S, Camm AJ, Saksena S, et al. International consensus on nomenclature and classification of atrial fibrillation: A collaborative project of the Working Group on Arrhythmias and the Working Group of Cardiac Pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. J Cardiovasc Electrophysiol 2003;14:443-5.
13. Cox JL. Surgical treatment of atrial fibrillation: A review. Europace 2004;5(Suppl 1):S20-9.
14. Slocum J, Byrom E, McCarthy L, Sahakian A, Swiryn S. Computer detection of atrioventricular dissociation from surface electrocardiograms during wide QRS complex tachycardias. Circulation 1985;72:1028-36.
15. Welch PD. The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. IEEE Trans Audio Electroacoustics 1967;15:70-3.

16. Bollmann A, Husser D, Stridh M, et al. Frequency measures obtained from the surface electrocardiogram in atrial fibrillation research and clinical decision-making. J Cardiovasc Electrophysiol 2003;14(10 Suppl):S154-61.
17. Bollmann A, Husser D, Olsson SB. Atrial fibrillatory frequency, atrial fibrillatory rate, or atrial cycle length – does it matter? Am J Cardiol 2004;94:147.
18. Stridh M, Sörnmo L, Meurling CJ, Olsson SB. Characterization of atrial fibrillation using the surface ECG: Time-dependent spectral properties. IEEE Trans Biomed Eng 2001;48:19-27.
19. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89:1665-80.
20. Gaita F, Riccardi R, Calò L, et al. Atrial mapping and radiofrequency catheter ablation in patients with idiopathic atrial fibrillation. Electrophysiological findings and ablation results. Circulation 1998;97:2136-45.
21. Sasaki T, Niwano S, Sasaki S, et al. Long-term follow-up of changes in fibrillation waves in patients with persistent atrial fibrillation: Spectral analysis of surface ECG. Circ J 2006;70:169-73.
22. Savino JS, Floyd TF, Cheung AT. Cardiac anesthesia. In: Cohn LH, Edmunds LH Jr, eds. Cardiac Surgery in the Adult, 2nd edn. New York: McGraw-Hill, 2003:249-81.
23. Bollmann A, Wodarz K, Esperer HD, Toepffer I, Klein HU. Response of atrial fibrillatory activity to carotid sinus massage in patients with atrial fibrillation. Pacing Clin Electrophysiol 2001;24:1363-8.
24. Fujiki A, Nagasawa H, Sakabe M, et al. Spectral characteristics of human atrial fibrillation waves of the right atrial free wall with respect to the duration of atrial fibrillation and effect of class I antiarrhythmic drugs. Jpn Circ J 2001;65:1047-51.
25. Bollmann A, Mende M, Neugebauer A, Pfeiffer D. Atrial fibrillatory frequency predicts atrial defibrillation threshold and early arrhythmia recurrence in patients undergoing internal cardioversion of persistent atrial fibrillation. Pacing Clin Electrophysiol 2002;25:1179-84.

2.1.1. Atriales Remodeling und Ergebnisse der chirurgischen Ablation

Grubitzsch H, Menes A, Modersohn D, Konertz W.

The role of atrial remodeling for ablation of atrial fibrillation.

Ann Thorac Surg. 2008; 85: 474-80.

Zusammenfassung der Ergebnisse

In dieser Studie wurden 73 Patienten (49,3% männlich, Alter 66±9,1 Jahre) mit permanentem Vorhofflimmern (mittlere Dauer 47±60,9 Monate), bei denen eine Vorhofablation im Zusammenhang mit einem Mitralklappeneingriff durchgeführt wurde, untersucht. Das atriale Remodeling wurde auf elektrischer (AFZL aus dem Oberflächen-EKG, siehe 2.1.1.), kontraktiler (an rechtsatrialen Myokardpräparaten bestimmte Kontraktionskraft) und struktureller Ebene (echokardiografisch bestimmter linksatrialer Durchmesser) analysiert. Zur letzten Nachuntersuchung (im Mittel nach 12±6,9 Monaten) wiesen 47 Patienten (71,2%) einen Sinusrhythmus auf, 41 (62,1%) ohne Antiarrhythmika. Das elektrische (AFZL 126-247 ms), kontraktile (Kontraktionskraft 2-18 mN/mm^2) und strukturelle Remodeling (linksatrialer Durchmesser 37-79 mm) zeigte eine breite interindividuelle Variabilität, aber keine Korrelationen zwischen den verschiedenen Ebenen. Auch zwischen Remodeling und Dauer des Vorhofflimmmerns bzw. linksatrialer hämodynamischer Last (LVEDP bzw. PCWP) bestand keine Beziehung. Die erfolgreiche Wiederherstellung des Sinusrhythmus war in der univariaten Analyse mit höherer Kontraktionskraft (7±4,2 versus 4±2,8 mN/mm^2, p=0,078), geringerem linksatrialen Durchmesser (51±7,1 versus 58±10,2 mm, p<0,05) und kürzerer Dauer des Vorhofflimmerns (34±48,7 versus 73±63,0 Monate, p<0,05) assoziiert, während sich in der binären logistischen Regressionsanalyse die Dauer des Vorhofflimmerns (odds ratio [OR] 1,01, 95%-Konfidenzinterval [KI] 1,00-1,02, p=0,045) und der linksatriale Durchmesser (OR 1,12, 95%-KI 1,02-1,23, p=0,016) als signifikante Parameter erwiesen.

Somit ist strukturelles, aber nicht elektrisches bzw. kontraktiles Remodeling neben der präoperativen Dauer des Vorhofflimmerns ein Prädiktor für die Wiederherstellung von Sinusrhythmus nach begleitender Vorhofablation bei Mitralklappeneingriffen.

The Role of Atrial Remodeling for Ablation of Atrial Fibrillation

Herko Grubitzsch, MD, Alexandro Menes, MD, Diethelm Modersohn, MD, PhD, and Wolfgang Konertz, MD, PhD

Department of Cardiovascular Surgery, Charité–Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

Background. **Atrial fibrillation (AF) causes electrical, contractile, and structural remodeling of the atria. We investigated remodeling in patients undergoing AF ablation.**

Methods. **Concomitant ablation of permanent AF, lasting 1 to 240 months, was performed in 73 patients (49.3% men) with a mean age of 66 ± 9.1 years undergoing mitral valve operations. Electrical (AF cycle length from surface electrocardiogram), contractile (force of contraction measured at right atrial muscle bundles), and structural (left atrial [LA] diameter from echocardiography) remodeling was assessed. Predictors for rhythm outcome were determined.**

Results. **Two patients died perioperatively, and 3 died during follow-up. The deaths were not ablation related. At the last follow-up (mean, 12 ± 6.9 months), 47 patients (71.2%) were in sinus rhythm, 41 (62.1%) without antiarrhythmic drugs. Corresponding to cycle length (126 to 247 ms), force (2 to 18 mN/mm^2), and LA diameter (37 to 79 mm), atrial remodeling exhibited a wide interindividual variability but no correlation between different remodeling levels. No relationship was found between remodeling and AF duration or LA hemodynamic load. Univariate analysis demonstrated higher force (7 ± 4.2 vs 4 ± 2.8 mN/mm^2, $p = 0.078$), smaller LA diameter (51 ± 7.1 vs 58 ± 10.2 mm, $p < 0.05$), and shorter AF duration (34 ± 48.7 vs 73 ± 63.0 months, $p < 0.05$) associated with successful sinus rhythm restoration, whereas logistic regression analysis revealed AF duration (odds ratio, 1.01; 95% confidence interval, 1.00 to 1.02, $p = 0.045$) and LA diameter (odds ratio, 1.12; 95% confidence interval, 1.02 to 1.23, $p = 0.016$) as predictors.**

Conclusions. **Atrial remodeling exhibited a high interindividual variability but no relationship within different remodeling levels, with AF duration or with LA hemodynamic load. However, AF duration and structural remodeling, but not electrical or contractile remodeling, predicted rhythm outcome.**

(Ann Thorac Surg 2008;85:474–80)

Atrial fibrillation (AF), the most frequent sustained atrial arrhythmia, is associated with an increased risk of stroke and premature death [1, 2]. A significant number of patients requiring cardiac operations, especially mitral valve operations, present with AF [3, 4]. The surgical approach to the treatment of AF was initially introduced as Maze procedure [5]. During the past decade, a less complex operation for concomitant AF treatment using different technologies for tissue ablation and focusing the lesion pattern on the left atrium was developed [6, 7]. Thus, sinus rhythm can be restored in approximately 80% of patients undergoing mitral valve operations and AF ablation [4, 8].

With time, AF induces several changes in atrial myocardium at electrophysiologic, contractile, and structural levels summarized as atrial remodeling and suggested to cause the progression of the arrhythmia [9]. In addition to shortened atrial refractoriness and reduced conduction velocity, a rise in the atrial fibrillatory rate, which can be determined from a surface electrocardiogram (ECG), is characteristic of electrical remodeling [9, 10]. Loss of contractility is the central finding of contractile remodeling [9]. On a cellular level, AF-induced structural changes include increased cell size, accumulation of glycogen, loss of sarcomeres, altered connexin expression, and fragmentation of sarcoplasmic reticulum, among others, whereas macroscopically, structural remodeling is characterized by left atrial dilatation [9].

With reports on depressed atrial contractility in AF patients undergoing cardiac operations [11] or on the predictive role of atrial fibrillatory rate for sinus rhythm conversion after medical AF treatment [12, 13], assessment of atrial remodeling came into focus in clinical medicine. It was postulated that individual quantification of the remodeling process might be useful for predicting treatment efficacy [10]. This study investigated atrial remodeling in patients undergoing mitral valve operations and concomitant AF ablation.

Patients and Methods

Patients and Surgical Procedures

Between January 2003 and February 2006, 73 consecutive patients (49.3% male) with a mean age of 66 ± 9.1 years scheduled for mitral valve operations underwent concomitant AF ablation. All patients had permanent/continuous AF according to established definitions [14, 15], and 11 (15.1%) had a history of thromboembolic events. After obtaining approval of the local Ethics Committee

Accepted for publication Sept 25, 2007.

Address correspondence to Dr Grubitzsch, Klinik für Kardiovaskuläre Chirurgie, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Charité-Platz 1, Berlin, 10117, Germany; e-mail: herko.grubitzsch@charite.de.

Published by Elsevier Inc

0003-4975/08/$34.00
doi:10.1016/j.athoracsur.2007.09.047

Table 1. Surgical Procedures

Procedure	Frequency No.	%
MVP	22	30.1
Isolated MVP	8	36.4
MVP + CABG	11	50.0
MVP + TVP/R	1	4.5
MVR + CABG + TVP/R	1	4.5
MVP + cor triatriatum correction	1	4.5
MVR	51	69.9
Isolated MVR	35	68.6
MVR + CABG	8	15.7
MVR + TVP/R	6	11.8
MVR + CABG + TVP/R	1	2.0
MVP + ASD closure	1	2.0
Left atrial reduction plasty	3	4.1
Reoperation	7	9.6

ASD = atrial septal defect; CABG = coronary artery bypass grafting; MVP = mitral valve plasty; MVR = mitral valve replacement; TVP/R = tricuspid valve plasty/replacement.

and individual informed consent for the study, preoperative, perioperative, and follow-up data were prospectively entered into an institutional database. Data were retrospectively analyzed.

The detailed procedures of the study cohort are listed in Table 1. Isolated mitral valve surgery was performed in 58.9% (43 of 73) of the patients. For patients who had valve replacement, biologic prostheses were implanted in 84.3% (43 of 51). Standard normothermic cardiopulmonary bypass and warm antegrade blood cardioplegia were used for all procedures.

The ablation concept used has been described in detail previously [8]. All patients underwent endocardial ablation of the left atrium. Microwave (Flex 4, Guidant Corp, Santa Clara, CA) energy was applied in 42 patients (57.5%) and radiofrequency (Cardioblate, Medtronic Inc, Minneapolis, MN) energy was used in 31 (42.5%), depending on device availability or surgeon's discretion. The lesion pattern consisted of (1) a box lesion isolating all pulmonary vein ostia, (2) a line into the left atrial appendage, and (3) a line to the mitral valve annulus (P3). The left atrial appendage was oversewn only if there were thrombi inside (n = 2). The probe for transesophageal echocardiography was removed during ablation to avoid esophageal injury.

Perioperative Course and Follow-Up

All patients were anticoagulated with heparin, followed by phenprocoumon, with a target international normalized ratio (INR) of 2.0 to 3.0. After 3 months and stable sinus or atrial-driven pacemaker rhythm in Holter ECG and mechanical atrial function in echocardiogram, anticoagulation treatment was discontinued. Patients with mechanical valve substitutes remained on permanent phenprocoumon therapy (target INR, 3.0 to 4.0). Direct current (DC) shock cardioversion of early recurrent AF was performed if a patient was symptomatic or hemodynamically compromised. Perioperatively, either patient's preoperative medication (β-blocker) was continued or antiarrhythmic treatment with class III antiarrhythmic drugs (sotalol or amiodarone) was initiated. The decision was left to the discretion of the surgeon. After discharge, the patient's family physician or cardiologist managed the anticoagulation and antiarrhythmic therapy.

Prospective follow-up was after 3, 6, and 12 months, and annually thereafter. Patients were interviewed and underwent clinical, electrocardiographic, and echocardiographic examination. At the 3- and 12-month follow-up, heart rhythm was monitored by 24-hour Holter ECG. In only 3 patients (4.2%), who were not able to visit the clinic, interviewing was done by telephone, and echocardiographic data were obtained from the referring cardiologist. Any regular atrial-driven rhythm, including atrioventricular (n = 1) and atrial-triggered ventricular (n = 1) pacing, was regarded as sinus rhythm.

Echocardiography

Preoperatively, before discharge and at follow-up, all patients underwent transthoracic echocardiographic examination using the HP Sonos 5500 (Hewlett Packard, Andover, MA). Left atrial and left ventricular (LV) diameter were measured using standard techniques. Left ventricular ejection fraction (LVEF) was assessed by the Simpson method. The presence of mechanical left atrial function was checked using the pulsed-wave signal of diastolic transmitral flow. Maximal flow velocities of E and A waves were measured and the E/A ratio was calculated. Quantification of atrial contractility by transesophageal echocardiography was beyond the scope of this study.

Assessment of Atrial Remodeling

Atrial fibrillatory activity allows individual quantification of electrical remodeling and can be reliably obtained from surface potentials [10]. Before operation, mean fibrillatory rate and corresponding atrial fibrillatory cycle length (AFCL) were determined using a high-gain, high-resolution surface ECG (CardioLink, Getemed, Teltow, Germany). After QRST cancellation, the resulting atrial ECG was down-sampled to 50 Hz, and spectral analysis was performed by fast-Fourier transform. The resulting power spectrum was analyzed in the 3- to 12-Hz (180 to 720 fibrillations/min [fpm]) range. The peak frequency component was converted to the dominant AFCL (AFCL [ms] = 60,000 [ms]/fibrillatory rate [fpm]).

After obtaining additional informed consent, specimens of right atrial appendages were excised before starting cardiopulmonary bypass for assessment of atrial contractile remodeling. Right atrial force of contraction certainly reflects the specific contractile remodeling due to AF, whereas left atrial contractility is also influenced by hemodynamic load (mitral valve disease).

The specimens were placed into cold cardioplegic solution (pH 7.4) containing 2,3-butane-dione-monoxime and delivered to the laboratory immediately. After equilibrating at room temperature, thin myocardial muscle bundles (length, 4 to 10 mm) in parallel with the muscle fiber direction were prepared under microscopic control. The average diameter and corresponding cross sectional

Table 2. Atrial Remodeling

	AF Duration (months)			PCWP/LVEDP (mm Hg)		
Remodeling[a]	≤12 (n = 29)	13–24 (n = 13)	>24 (n = 31)	≤10 (n = 22)	11–20 (n = 34)	>20 (n = 17)
Electrical						
AFCL, ms	157 ± 15.1	147 ± 14.4	156 ± 19.9	154 ± 16.6	152 ± 17.0	157 ± 20.9
Contractile						
Force, mN/mm^2	6 ± 2.5	6 ± 6.9	7 ± 4.1	6 ± 4.8	6 ± 3.2	6 ± 2.6
Structural						
LA diameter, mm	52 ± 9.8	51 ± 11.8	54 ± 8.1	50 ± 7.2	54 ± 8.4	55 ± 13.8

[a] Data are presented as mean ± standard deviation.

AF = atrial fibrillation; AFCL = atrial fibrillation cycle length; LA = left atrial; LVEDP = left ventricular end-diastolic pressure; PCWP = pulmonary capillary wedge pressure.

area were 0.45 ± 0.03 mm and 2.3 ± 0.15 mm^2, respectively. The muscle strips were placed in an organ bath filled and perfused (1 to 2 mL/min) with prewarmed (37°C) modified Tyrode solution (pH 7.4, continuously gassed with 95% oxygen and 5% carbon dioxide), fixed to the chamber with a hanger and attached to a precalibrated force transducer with a silk loop and a stainless steel hook.

After an equilibration period of 20 minutes, the muscles were stretched to nearly 1.0 mN. External field stimulation was performed with rectangular pulses (5 ms, 5% to 10% above threshold) at 1 Hz. Resting tension was increased stepwise by 0.1 mN until the muscle length providing maximal active force generation was reached (L_{max} 5.1 ± 0.2 mm). Force of contraction (force) was determined before and after an equilibration period of 30 minutes. Two muscle preparations that showed a force of less than 1.0 mN or a force decline exceeding 5% during this period were excluded from the study.

The left atrial diameter was used as measure for structural remodeling. It was determined by echocardiography using M-mode measurement in the parasternal long axis.

Statistical Analysis

Unless otherwise indicated, data are presented as mean ± standard deviation or absolute and relative frequencies. For comparison between groups, the nonparametric Mann-Whitney test was used for continuous variables and the χ^2 test for categoric variables. For comparison of follow-up and preoperative data within groups, the nonparametric Wilcoxon rank sum test was applied. Covariation between different remodeling parameters was analyzed by the Pearson product-moment correlation coefficient (r) and the coefficient of determination (r^2). Binary logistic regression analysis was used for identifying factors predicting sinus rhythm conversion. Factors found significant ($p < 0.1$) on univariate testing were entered in the multivariate analysis to identify independent risk factors. The odds ratios (OR), 95% confidence intervals (CI), and p values were calculated for each risk factor. During follow-up, freedom from recurrent AF was calculated according to the Kaplan-Meier method, and differences were analyzed by log-rank test. All tests of significance were two-tailed, and a value of $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS 13.0 software (SPSS Inc, Chicago, IL).

Results

Baseline Data of the Study Cohort

AF duration was 47 ± 60.9 months (range, 1 to 240 months). At baseline, patients were in New York Heart Association (NYHA) functional class 3.0 ± 0.70 (range, I to IV), but presented mostly with normal LV function

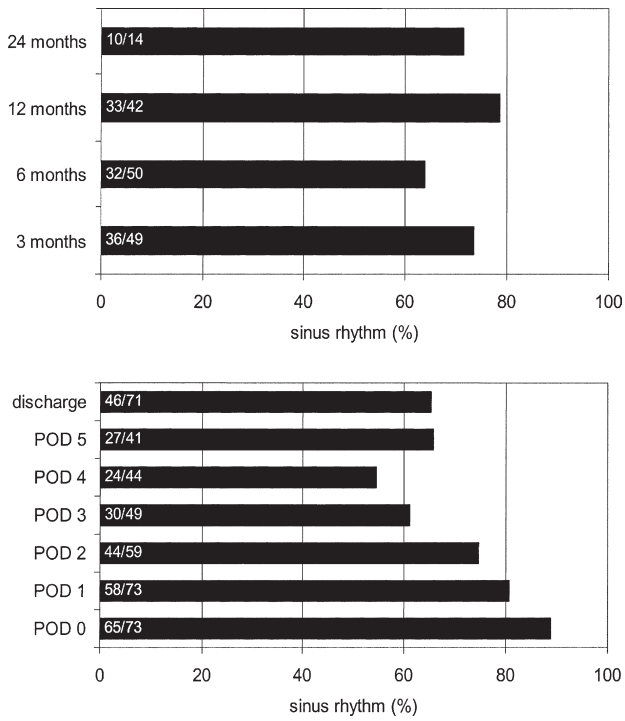

Fig 1. Prevalence of sinus rhythm. The lower graph depicts the sinus rhythm conversion rate immediately after operation, whereas the upper graph shows the sinus rhythm conversion rate during follow-up. Figures in the bars indicate absolute frequencies of patients with sinus rhythm. (POD = postoperative day.)

Table 3. Follow-Up Data

Variable[a]	SR (n = 47)	Non-SR (n = 19)	*p* Value
Patients with palpitations	2 (4.2)	5 (26.3)	0.008
NYHA class	1.7 ± 0.62	2.1 ± 0.32	0.010
LVEF	0.51 ± 0.11	0.47 ± 0.188	0.287
LVEDD, mm	52 ± 9.4	56 ± 12.6	0.296
Left atrial diameter, mm	42 ± 6.2	44 ± 6.5	0.856
Medication			
β-blocker	38 (80.8)	14 (73.7)	0.519
Digitalis	11 (23.4)	7 (36.8)	0.267
Class III antiarrhythmic drugs	6 (12.8)	3 (15.8)	0.746

[a] Categoric data are presented as number (%) and continuous data as mean ± standard deviation.

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SR = sinus rhythm.

according to LVEF (0.51 ± 0.11; range, 0.20 to 0.79) and left ventricular end-diastolic diameter (LVEDD; 55 ± 8.2 mm; range, 36 to 71 mm). Etiology of mitral valve disease was degenerative in 36 patients (49.3%), rheumatic in 23 (31.5%), and functional in 14 (19.2%). Valvular dysfunction was regurgitation in 50 patients (68.5%), mixed lesion in 18 (24.7%), and stenosis in 5 (6.8%). The left atrial hemodynamic load, as referred to left ventricular end-diastolic pressure (LVEDP) or pulmonary capillary wedge pressure (PCWP), was 15 ± 6.8 mm Hg (range, 3 to 38 mm Hg). Coronary artery disease was present in 29 patients (39.7%), pulmonary hypertension in 52 (71.2%), and 11 (15.1%) had a history of thromboembolic events. When evaluated by the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), expected perioperative mortality was 9.6% ± 11.35% (range, 1.5% to 61.7%).

Perioperative Course and Follow-Up

Overall, respective times for aortic cross-clamp, cardiopulmonary bypass, and operation were 78 ± 20.8, 110 ± 29.2, and 198 ± 50.9 minutes. Patients were discharged from the hospital after 12 ± 11.3 days. Perioperative morbidity was characterized by reexploration for bleeding in 1 patient, late pericardial effusion in 2, heart failure in 6 necessitating intraaortic balloon pump support in 3 and temporary left ventricular assist device placement in 1, renal failure in 2, and intracerebral hemorrhage in 1. No thromboembolic events occurred. Two patients (2.7%) died within 30 days of operation of cardiac and multiple organ failure. The ablation procedure itself did not cause any injury or death.

Mean follow-up was after 12 ± 6.9 months. Two patients (2.8%) were lost to follow-up, and 3 (4.2%) died, 1 each of heart failure, sudden cardiac death, and multiple organ failure after major abdominal surgery.

Atrial Remodeling

Atrial remodeling was characterized by a wide interindividual variability on electrical (AFCL, 156 ± 22.1 ms; range, 126 to 247 ms), contractile force (6 ± 3.9 mN/mm^2; range, 2 to 18 mN/mm^2), and structural level (left atrium diameter, 53 ± 9.0 mm; range, 37 to 79 mm). Table 2 illustrates that there was no relationship between AF duration, left atrial hemodynamic load, or measures of remodeling. Furthermore, using covariation analysis, we were unable to detect any association within remodeling criteria between AFCL and force ($r = -0.134$, $r^2 = 0.018$, $p = 0.290$), between AFCL and left atrial diameter ($r = 0.054$, $r^2 = 0.003$, $p = 0.668$), or between force and left atrial diameter ($r = 0.221$, $r^2 = 0.05$, $p = 0.174$).

Rhythm Outcome

Figure 1 shows the sinus rhythm prevalence for the overall cohort immediately after operation and during follow-up. Direct current shock cardioversion was performed in 4 patients before discharge and in 2 during follow-up. After 4 months, 1 patient underwent successful interventional ablation of left atrial flutter that was caused by an incomplete mitral isthmus line. Pacemakers were implanted in 3 patients early and in 2 late after operation. At

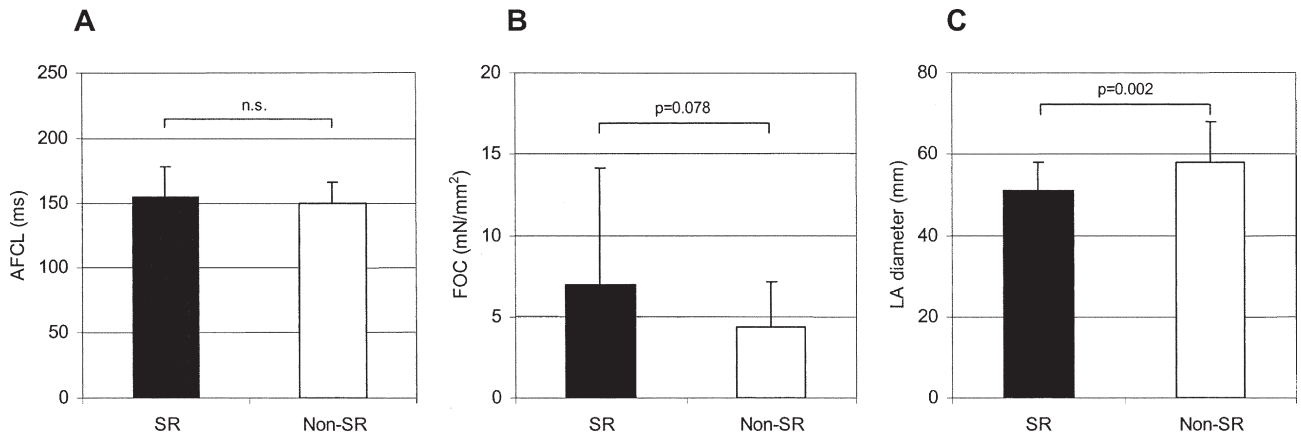

Fig 2. Rhythm outcome and atrial remodeling. The graphs show the relationship of (A) electrical, (B) contractile, and (C) structural remodeling and rhythm outcome at the latest follow-up. The range bars show the standard deviation. (AFCL = atrial fibrillatory cycle length; FOC = force of contraction; LA = left atrial; SR = sinus rhythm.)

Table 4. Rhythm Outcome and Clinical Characteristics

Variable[a]	SR (n = 47)	Non-SR (n = 19)	*p* Value
Age, y	65 ± 10.3	67 ± 6.0	0.712
Female sex	25 (53.2)	8 (42.1)	0.415
Body surface area, m^2	1.8 ± 0.20	1.8 ± 0.19	0.840
NYHA class	3.0 ± 0.74	3.0 ± 0.58	0.875
AF duration, mon	34 ± 48.7	73 ± 63.0	<0.05
LVEF	0.52 ± 0.114	0.51 ± 0.106	0.577
LVEDD, mm	55 ± 6.0	55 ± 11.0	0.899
PCWP/LVEDP, mm Hg	14 ± 7.3	15 ± 4.8	0.543
Valvular pathology			0.422
Stenosis	2 (4.2)	2 (10.5)	
Regurgitation	32 (68.1)	14 (73.7)	
Mixed lesion	13 (27.6)	3 (15.8)	
Etiology			0.139
Rheumatic	14 (29.8)	5 (26.3)	
Degenerative	21 (44.7)	13 (68.4)	
Functional	11 (23.4)	1 (5.3)	
Coronary artery disease	23 (48.9)	4 (21.0)	0.037
Previous embolism	8 (17.0)	2 (10.5)	0.505
Logistic EuroSCORE	7.8 ± 9.20	10.0 ± 9.18	0.133
Valvular procedure			0.185
MV plasty	16 (34.0)	4 (21.1)	
MV replacement	31 (66.0)	15 (78.9)	
LA reduction plasty	2 (4.2)	1 (5.3)	0.575
Ablation technology			0.092
Microwave	24 (51.1)	14 (73.7)	
Radiofrequency	23 (48.9)	5 (26.3)	
Aortic cross clamp time, min	80 ± 17.8	74 ± 29.1	0.103
Class III antiarrhythmic drugs	25 (53.2)	10 (52.6)	0.786

[a] Categoric data are presented as number (%), and continuous data as mean ± standard deviation.

AF = atrial fibrillation; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; MV = mitral valve; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; SR = sinus rhythm.

last follow-up, 47 patients (71.2%) were in sinus rhythm, 41 (62.1%) without antiarrhythmic drugs. Characteristic follow-up data are listed in Table 3. Sinus rhythm was associated with improved outcome in NYHA functional class and palpitations. According to transmitral diastolic flow pattern (pulsed-wave Doppler signal), 80.5% of patients with sinus rhythm exhibited normal atrial contraction with an E/A ratio of 2.5 ± 1.01.

Predictors for Rhythm Outcome

The association of sinus rhythm conversion and measures of atrial remodeling is shown in Figure 2. Whereas the preoperative left atrial diameter was significantly smaller and atrial contractility somewhat greater in patients regaining sinus rhythm, AFCL demonstrated no difference in rhythm outcome. Analysis of the relationship between clinical characteristics and successful AF treatment (Table 4) shows that patients who were in sinus rhythm at last follow-up exhibited significantly shorter preoperative AF duration and presented more frequently with coronary artery disease. In patients without sinus rhythm, there was a nonsignificant trend towards the use of microwave technology for ablation. Logistic regression analysis of factors found significant in univariate testing (AF duration, force, left atrial diameter, presence of coronary artery disease, and ablation technology) revealed only AF duration (OR. 1.01; 95% CI, 1.00 to 1.02; $p = 0.045$) and left atrial diameter (OR, 1.12; 95% CI, 1.02 to 1.23; $p = 0.016$) as independent risk factors for AF persistence. Kaplan-Meier estimates (Fig 3)

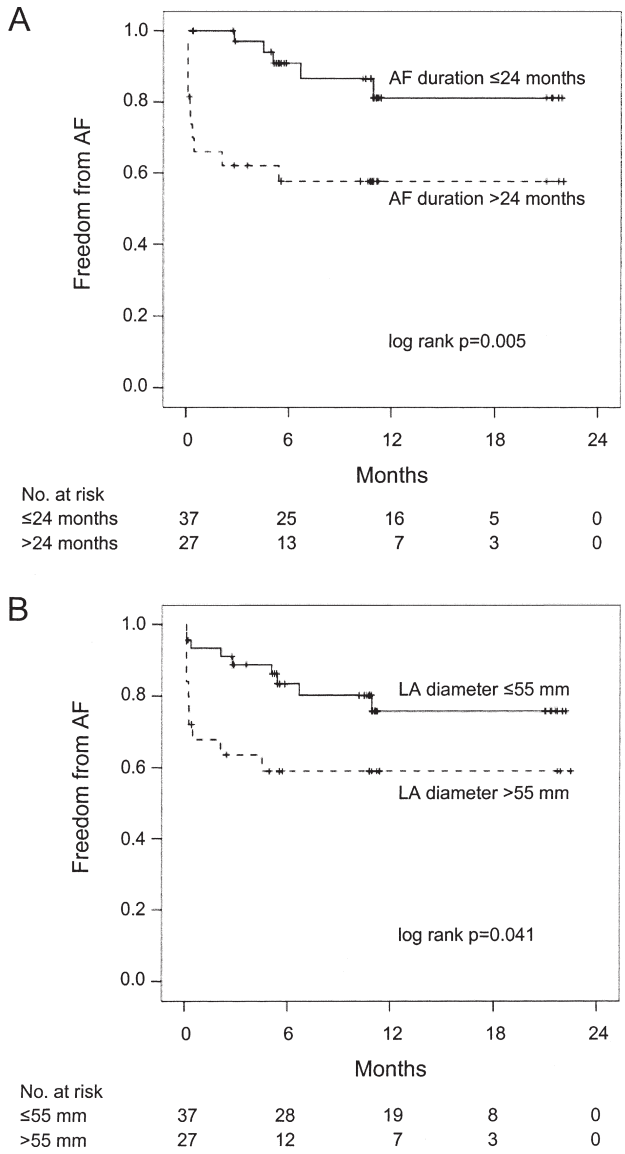

Fig 3. Kaplan-Meier estimates. Freedom from atrial fibrillation (AF) according to (A) preoperative AF of 24 months or less (solid line) and exceeding 24 months duration (dashed line), and (B) left atrial (LA) size of 55 mm or less (solid line) and diameter exceeding 55 mm (dashed line).

illustrate that freedom from recurrent AF significantly depended on preoperative AF duration and structural remodeling of the left atrium.

Comment

AF frequently accompanies structural heart disease and occurs in approximately 5% of patients with mitral valve disease per year [3]. Its progressive nature results from electrical, contractile, and structural remodeling of the atria induced by the underlying heart disease and the arrhythmia itself [9]. Individual quantification of the remodeling process was postulated to be useful for predicting treatment efficacy [10]. In this study we investigated atrial remodeling in AF and mitral valve disease and its influence on results of AF ablation.

In addition to preoperative AF duration, we found structural remodeling (left atrial dilatation) predictive for rhythm outcome after AF ablation. In contrast, electrical and contractile remodeling exhibited no influence according to the multifactorial model. For remodeling in general, we were not able to detect any association with AF duration or left atrial hemodynamic load, and we found no relationship among the measures of electrical, contractile, or structural remodeling.

Undoubtedly, compared with sinus rhythm, AF is associated with remarkable alterations on the electrical, contractile, and structural level [9, 11, 16, 17]. During the transition from sinus rhythm to paroxysmal AF and further on to persistent AF, a shortening of the atrial effective refractory period, a reduced conduction velocity, and a rise in atrial fibrillatory rate were shown to be characteristic of electrical remodeling [16, 17]. In persistent AF, a lower frequency was observed with shorter compared with longer AF duration, and the mean AFCL decreased significantly over time [12, 18]. Very recently we found a nonsignificant trend towards shorter AFCL, with longer AF duration in a subset of 52 patients with persistent AF [unpublished data].

A reason why this and other reports [17] have failed to demonstrate a relationship between AF duration and fibrillation frequency could be that AFCL in longer-lasting AF (>3 months) is often near the physiologic frequency limit, rendering detection of significant differences difficult. Some studies showed that atrial fibrillatory frequency predicted sinus rhythm conversion after treatment with antiarrhythmic drugs [12, 13]. It can be concluded from these reports that the "AF conversion threshold" ranges between 250 and 300 ms of AFCL with drug-induced frequency reduction. The cycle length in our patients who either regained sinus rhythm (155 ± 23.2 ms) or did not (150 ± 16.0 ms) was far from this threshold and did not exceed 247 ms at baseline, which may explain why we were not able to demonstrate an influence on sinus rhythm conversion.

Compared with sinus rhythm (data not shown), atrial contractility was significantly depressed in patients with persistent AF; this is probably due to quantitative or functional changes, or both, of the L-type Ca^{2+} channel [11]. Echocardiographic studies after cardioversion have shown that atrial contractile dysfunction recovered completely within 24 hours of sinus rhythm when AF lasted 2 weeks, whereas recovery took more than 1 month when AF lasted more than 6 weeks [19]. We, however, were unable to demonstrate a relationship between force and AF duration; furthermore, contractility was not associated with other remodeling parameters or hemodynamic stress. As for AFCL, detection of significant differences or relationships might have failed because contractile dysfunction was advanced and near its nadir. Regarding the lack of any association between contractility and left atrial load, it should be taken into account that force was measured on right atrial tissue. The weak trend in univariate analysis toward better atrial contractility in patients who regained sinus rhythm (Fig 2) could reinforce the idea that AF could be easier to terminate in patients with an earlier stage of contractile remodeling.

AF-dependent loss of contractility causes atrial dilatation, the most prominent sign of structural remodeling [20] and vice versa, enlargement and the associated fibrosis of the atria perpetuate the susceptibility to AF [9]. This vicious circle is exacerbated by mitral valve disease, which by left atrial pressure increase stimulates left atrial dilatation, explaining its association with AF [3].

Structural remodeling usually develops after months, whereas electrical and contractile remodeling occurs immediately after AF initiation [9]. Similarly, electrical remodeling after reestablishing sinus rhythm reverses rapidly and completely, whereas renormalization of structural remodeling takes time and is possibly incomplete [21]. Therefore, it was hypothesized that structural changes are an important factor for the development of permanent AF [9]. Recent reports [8, 13, 22–24] and our findings (Fig 3B) strongly suggest that they are an important predictor for AF termination as well.

Although well-defined animal experiments of short-term AF were able to demonstrate a close relation between different levels of remodeling [25], clinical studies have failed to do so [12]. As in our patients, a high interindividual variability in remodeling measures and AF duration, as well as the presence of additional patient- and disease-related factors, apparently hamper the detection of any supposed relationship.

Our results of 71% sinus rhythm (62% without antiarrhythmic drugs) are in line with other reports of 60% to 80% sinus rhythm [4], although we used a strict left atrial approach in contrast to the classical biatrial approach. Because it was shown that AF will not recur if macroreentry can be prevented by lesions critically placed in the left atrium [6, 15], a less complex procedure might be beneficial, particularly for concomitant AF treatment.

Freedom from recurrent AF during follow-up was greater in patients with AF lasting less than 2 years and a left atrial diameter smaller than 55 mm (Fig 3). Patients who were in sinus rhythm at follow-up had significantly fewer palpitations. They were also in a better NYHA functional class, although left ventricular function was comparable in patients with and without sinus rhythm (Table 3). These data suggest that reestablishing sinus rhythm in fact attenuates AF sequelae.

The study has some limitations. Because left atrial size was renormalized irrespective of rhythm outcome, interpretation of our results must not ignore primary cardiac surgery. This might account for restoration and maintenance of sinus rhythm just as for any other detected symptomatic improvement, but we are unable to assess its relative contribution vs the ablation procedure itself. However, patients with or without sinus rhythm had undergone similar mitral valve procedures (Table 4). Fibrillation frequency, force, and left atrial diameter are not the only variables that change due to AF; however, they are characteristics that can be easily assessed and are able to predict the response to AF treatment [10, 11]. In fact, we simultaneously investigated electrical, contractile, and structural remodeling in patients undergoing AF ablation. To add weight to our findings, we did not include patients with paroxysmal/intermittent AF. Nonetheless, heterogeneity within our cohort resulting from the variability of patient- or disease-related factors such as age or AF duration has to be considered.

Owing to its design, the study has the general limitations inherent in noncontrolled observational studies. Procedure-related bias is considered negligible because all surgeons used an identical lesion pattern. Moreover, it was demonstrated that results do not depend on surgeon's experience or energy source used for tissue ablation [7, 26].

In conclusion, sinus rhythm could be restored in 71% of patients (62% without antiarrhythmic drugs) undergoing mitral valve surgery and concomitant AF ablation. Atrial remodeling exhibited a high interindividual variability. No relationship existed between remodeling, AF duration, or left atrial hemodynamic load, or between measures of electrical, contractile, or structural remodeling. However, rhythm outcome after AF ablation was independently predicted by AF duration and structural remodeling (left atrium size) but not by electrical or contractile remodeling.

Alexandro Menes was supported by a grant from the Deutscher Akademischer Austauschdienst (DAAD). We thank Doreen Boettner for excellent coordination of patients' follow up.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
2. Chesebro JH, Fuster V, Halperin JL. Atrial fibrillation–risk marker for stroke. N Engl J Med 1990;323:1556–8.
3. Grigioni F, Avierinos JF, Ling LH, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002;40:84–92.
4. Gillinov AM. Ablation of atrial fibrillation with mitral valve surgery. Curr Opin Cardiol 2005;20:107–14.
5. Cox JL, Schuessler RB, D'Agostino HJ Jr, et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569–83.
6. Kottkamp H, Hindricks G, Hammel D, et al. Intraoperative radiofrequency ablation of chronic atrial fibrillation: a left atrial curative approach by elimination of anatomic anchor reentrant circuits. J Cardiovasc Electrophysiol 1999;10:772–80.
7. Grubitzsch H, Beholz S, Dohmen P, Dushe S, Konertz W. Does energy modality determine results of atrial fibrillation ablation? Thorac Cardiov Surg 2007;55(suppl 1):71.
8. Grubitzsch H, Beholz S, Dohmen P, Dushe S, Liu J, Konertz W. Ablation of atrial fibrillation in valvular heart surgery: are results determined by underlying valve disease? J Heart Valve Dis 2007;16:76–83.
9. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodelling during atrial fibrillation. Cardiovasc Res 2002;54:230–46.
10. Bollmann A, Husser D, Stridh M, et al. Frequency measures obtained from the surface electrocardiogram in atrial fibrillation research and clinical decision making. J Cardiovasc Electrophysiol 2003;14(suppl):S154–61.
11. Schotten U, Ausma J, Stellbrink C, et al. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. Circulation 2001;103:691–8.
12. Bollmann A, Kanuru NK, McTeague KK, Walter PF, DeLurgio DB, Langberg JJ. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. Am J Cardiol 1998;81:1439–45.
13. Bollmann A, Binias KH, Toepffer I, Molling J, Geller C, Klein HU. Importance of left atrial diameter and atrial fibrillatory frequency for conversion of persistent atrial fibrillation with oral flecainide. Am J Cardiol 2002;90:1011–4.
14. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol 2006;48:e149–246.
15. Cox JL. Surgical treatment of atrial fibrillation: a review. Europace 2004;5:S20–9.
16. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
17. Bollmann A, Sonne K, Esperer HD, et al. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG. Cardiovasc Res 1999;44:60–6.
18. Sasaki T, Niwano S, Sasaki S, et al. Long-term follow-up of changes in fibrillation waves in patients with persistent atrial fibrillation–spectral analysis of surface ECG. Circ J 2006;70:169–73.
19. Manning WJ, Silverman DI, Katz SE, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994;23:1535–40.
20. Schotten U, de Haan S, Neuberger HR, et al. Loss of atrial contractility is primary cause of atrial dilatation during first days of atrial fibrillation. Am J Physiol Heart Circ Physiol 2004;287:H2324–H2331.
21. Ausma J, van der Velden HMW, Lenders MH, et al. Reverse structural and gag-junctional remodeling after prolonged atrial fibrillation in the goat. Circulation 2003;107:2051–8.
22. Gaynor SL, Schuessler RB, Bailey MS, et al. Surgical treatment of atrial fibrillation: predictors of late recurrence. J Thorac Cardiovasc Surg 2005;129:104–11.
23. Gillinov AM, Sirak J, Blackstone EH, et al. The Cox maze procedure in mitral valve disease: predictors of recurrent atrial fibrillation. J Thorac Cardiovasc Surg 2005;130:1653–60.
24. Chen MC, Chang JP, Chang HW, et al. Clinical determinants of sinus conversion by radiofrequency maze procedure for persistent atrial fibrillation in patients undergoing concomitant mitral valvular surgery. Am J Cardiol 2005;96:1553–7.
25. Schotten U, Allessie M. Electrical and contractile remodeling during atrial fibrillation go hand-in-hand. PACE 2001;24:572.
26. Grubitzsch H, Beholz S, Dohmen P, Dushe S, Liu J, Konertz W. Concomitant ablation of atrial fibrillation: are results associated with surgeon's experience? J Card Surg 2007;22:300–5.

2.2. Untersuchung klinischer Faktoren

An dem vergleichsweise homogenen Kollektiv von Patienten mit Mitralklappenerkrankungen und Vorhofflimmern konnte gezeigt werden, dass ausgehend von dem pathophysiologischen Konzept des atrialen Remodeling vor allem die strukturellen Veränderungen Einfluss auf die Ergebnisse der chirurgischen Ablation haben (2.1.2.). Welche Rolle andere Herzklappenerkrankungen für die Wiederherstellung des Sinusrhythmus spielen bzw. welche klinischen Faktoren die Zeit bis zum Wiederauftreten von Vorhofflimmern bestimmen, war Gegenstand weiterer Untersuchungen.

2.2.1. Herzklappenerkrankungen und Ergebnisse der chirurgischen Ablation

Grubitzsch H, Beholz S, Dohmen PM, Dushe S, Liu J, Konertz W.
Ablation of atrial fibrillation in valvular heart surgery: are results determined by underlying valve disease?
J Heart Valve Dis. 2007;16: 76-83.

Zusammenfassung der Ergebnisse

In dieser Studie wurden 124 Patienten (47,6% männlich, Alter 70±8,7 Jahre) mit permanentem Vorhofflimmern und Erkrankungen der Mitralklappe (n=64), der Aortenklappe (n=37) bzw. kombinierter Klappenerkrankung (n=23) untersucht. Bezogen auf Patienten mit Mitralklappenerkrankungen waren Patienten mit Aortenklappenerkrankungen durch höheres Alter ($p<0,001$) und geringere Vorhofdilatation ($p<0,05$) gekennzeichnet, während Patienten mit kombinierten Klappenerkrankungen vergleichbar waren. Die Sinusrhythmus-Konversion nach im Mittel 10 Monaten wurde in 76,8%, 63,3% und 58,8% der Patienten mit Mitral-, Aorten- bzw. kombinierten Klappenerkrankungen erreicht (n.s.). Patienten mit versus ohne erfolgreiche Sinusrhythmus-Konversion wiesen in der univariaten Analyse eine kürzere Vorhofflimmerdauer (42±49,0 versus 85±67,2 Monate, $p<0,05$) und eine geringere linksatriale Dilatation (50±8,1 versus 55±9,2 mm, $p<0,05$) auf, zeigten aber keine Unterschiede hinsichtlich der zugrundeliegenden Klappenerkrankung, des Alters, der

linksventrikulären Funktion bzw. des logistischen EuroSCORE. In der binären logistischen Regressionsanalyse erwiesen sich die Vorhofflimmerdauer (OR 1,01, 95%-KI 1,00-1,02, $p<0,05$) und der linksatriale Durchmesser (OR 1,08, 95%-KI 1,01-1,15, $p<0,05$) als unabhängige Prädiktoren für rekurrentes Vorhofflimmern. Von den Patienten, bei denen das Vorhofflimmern nicht länger als zwei Jahre bestanden hatte, waren zur Nachuntersuchung 86% im Sinusrhythmus.

Somit wird die Sinusrhythmus-Konversion nach Herzklappenchirurgie und Vorhofablation nicht vom zugrundeliegenden Klappenvitium, sondern von der Dauer der Arrhythmie und vom linksatrialen Durchmesser bestimmt. Da Vorhofflimmern nach erfolgreicher Ablation bei einigen Patienten im Verlauf auch erneut auftreten kann, war zu klären, welche Faktoren die Zeit bis zum Wiederauftreten bestimmen.

Ablation of Atrial Fibrillation in Valvular Heart Surgery: Are Results Determined by Underlying Valve Disease?

Herko Grubitzsch, Sven Beholz, Pascal M. Dohmen, Simon Dushe, Jianshi Liu, Wolfgang Konertz

Department of Cardiovascular Surgery, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

Background and aim of the study: **Although, in recent years, atrial fibrillation (AF) ablation has become an effective concomitant procedure in cardiac surgery, it is unclear whether the outcome of the procedure is determined by the underlying valve disease.**
Methods: **Between 2003 and 2005, 191 patients (100 females, 91 males; mean age 70 ± 8.7 years) underwent concomitant left atrial (LA) ablation. Among these patients, those with permanent AF (pAF) and mitral (MVD; n = 64), aortic (AVD; n = 37), and combined valve disease (CVD; n = 23) were prospectively studied after three, six and 12 months, and annually thereafter. The predictive values of preoperative variables for postoperative AF were examined.**
Results: **AVD patients were older than MVD patients (74 ± 7.8 versus 66 ± 8.6 years; p <0.001), and presented smaller atria (48 ± 5.7 versus 53 ± 8.0 mm; p <0.05), but CVD patients were similar to MVD patients in terms of these parameters (age 70 ± 9.3 years, LA diameter 54 ± 9.6 mm). Ablation caused no injury or death in any of the patients. Within 30 days after surgery, three (4.7%), three (8.1%) and two (8.7%) of the MVD, AVD and CVD patients, respectively, had died (6.4% overall mortality). The sinus rhythm (SR) conversion rate was 76.8, 63.3 and 58.8% (p = NS) after a mean follow up (FU) of 10 ± 4.0, 9 ± 4.2 and 10 ± 3.9 months (p = NS) in the MVD, AVD and CVD groups, respectively. FU was 97% complete. During FU, four (6.6%), two (5.9%) and four (19.0%) MVD, AVD and CVD patients died, respectively. Univariate analysis demonstrated a shorter AF duration (42 ± 49.0 versus 85 ± 67.2 months; p <0.05) and smaller LA diameter (50 ± 8.1 versus 55 ± 9.2 mm; p <0.05) in patients with SR versus non-SR. Multivariate analysis revealed AF duration (Odds ratio (OR) 1.01, 95% CI 1.00-1.02, p <0.05) and LA diameter (OR 1.08, 95% CI 1.01-1.15, p <0.05) as independent predictors of SR conversion. Overall, 86% of patients with two or less years' duration of pAF were in SR at FU.**
Conclusion: **AF duration and LA diameter, but not the type of valve disease, predict SR conversion after concomitant ablation of pAF in valvular heart surgery.**

The Journal of Heart Valve Disease 2007;16:76-83

Atrial fibrillation (AF) is associated with an increased risk of stroke and premature death (1,2). It is the most frequent sustained atrial arrhythmia, and affects a significant number of patients necessitating valvular heart surgery (1,3-5). During the past decade, the surgical treatment of AF, which initially was introduced as the maze procedure (6), has been developed to a less-complex operation by using different technologies for tissue ablation and by focusing the lesion pattern on the left atrium (7-9). The results of these approaches have shown great promise, but seem to depend on patient- and disease-related preoperative factors (10-12). Conflicting evidence exists regarding the importance of the underlying heart disease when AF ablation is performed as a concomitant procedure. Some authors have reported superior results in mitral as compared to non-mitral surgery (13,14), whereas others have not (5,15). Thus, in the present study the question was asked as to whether the results of left atrial ablation for AF treatment in concomitant valvular heart surgery are determined by the underlying valve disease.

Address for correspondence:
Dr. H. Grubitzsch, Klinik für Kardiovaskuläre Chirurgie, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Charité-Platz 1, 10117 Berlin, Germany
e-mail: herko.grubitzsch@charite.de

Clinical material and methods

Patients

Between January 2003 and December 2005, a total of 191 patients (100 females, 91 males; mean age 70 ± 8.7

years) who were scheduled for cardiac surgery underwent concomitant AF ablation. The preoperative, perioperative and follow up data were entered prospectively into an institutional database. Informed consent regarding the operation and data acquisition was obtained from all patients. Patients with permanent/continuous AF (pAF), according to established definitions (16,17), and mitral (MVD; n = 64), aortic (AVD; n = 37) or combined valve disease (CVD; n = 23) were analyzed retrospectively. Patients with paroxysmal/intermittent AF (n = 25) and isolated coronary artery disease (n = 42) were excluded from the study. Among MVD and AVD patients, the main valvular dysfunctions, respectively, were stenosis in four and 30, regurgitation in 42 and one, and mixed in 18 and six cases. CVD patients presented with combined aortic and mitral valve disease in 14 cases, with combined mitral and tricuspid valve disease in eight cases, and with combined aortic, mitral and tricuspid valve disease in one case. The logistic EuroSCORE (18) was determined in order to assess the perioperative risk.

Surgical procedure

The detailed surgical procedures of the study group are listed in Table I. Re-do surgery was performed in three, one and four patients in the MVD, AVD, and CVD groups, respectively. The majority of valve substitutes were biological prostheses. Except for pulmonary autografts and one mechanical valve (in one CVD patient), all other aortic valve substitutes were stentless biological prostheses. In six patients (five MVD, one CVD) the mitral valve was replaced with a mechanical substitute.

For all procedures, standard normothermic cardiopulmonary bypass and warm antegrade blood cardioplegia were used. All patients underwent endocardial ablation of the left atrium. Microwave (Flex 4®; Guidant Corporation, Santa Clara, CA, USA) or radiofrequency (RF) (Cardioblate®; Medtronic Inc., Minneapolis, MN, USA) energy was applied, depending on device availability or the surgeon's discretion. Each of these methods has been described in detail previously (7,8). Since it was known that AF would not recur if macro-reentry could be prevented by lesions placed critically in the left atrium (9,17), ablation was focused on the left side. The lesion pattern consisted of: (i) left atrial posterior wall ablation isolating all pulmonary vein ostia; (ii) a line into the left atrial appendage; and (iii) a line to the mitral valve annulus (P3). Since the left atrial appendage plays a role as a

Table I: Surgical procedures.

Condition	Absolute frequency (n)	Relative frequency	
		Overall (%)	Within-group (%)
Mitral valve disease	64	51.6	
Isolated MVR	36	29.0	56.2
Isolated MVP	8	6.4	12.5
MVR + CABG	8	6.4	12.5
MVP + CABG	10	8.1	15.6
MVR + ASD closure	1	0.8	1.6
MVP + cor triatriatum correction	1	0.8	1.6
Aortic valve disease	37	29.8	
Isolated AVR	28	22.6	75.7
Isolated Ross procedure	3	2.4	8.1
AVR + CABG	5	4.0	13.5
Ross procedure + CABG	1	0.8	2.7
Combined valve disease	23	18.5	
AVR + MVP/R	10	8.1	43.5
Ross procedure + MVP	1	0.8	4.3
AVR + MVP/R + CABG	3	2.4	13.0
MVP/R + TVP/R	6	4.8	26.1
MVP/R + TVP/R + CABG	2	1.6	8.7
AVR + MVP + TVP	1	0.8	4.3

ASD: Atrial septal defect; AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; MVP: Mitral valve plasty; MVR: Mitral valve replacement; TVP/R: Tricuspid valve plasty/replacement.

compliance chamber (which is especially important in heart failure) and contributes to atrial transport as well as to atrial natriuretic peptide secretion (19), it was oversewn only if it contained thrombi (n = 3). The transesophageal echocardiography (TEE) probe was removed during ablation in order to avoid esophageal injury.

Perioperative treatment

All patients were anticoagulated with heparin followed by phenprocoumon, with a target International Normalized Ratio (INR) of 2.0-3.0. After three months, anticoagulation was ceased if Holter ECG confirmed stable sinus rhythm (SR) or atrial-driven pacemaker rhythm and the echocardiogram showed mechanical atrial function. Those patients who had received mechanical valve substitutes were maintained on phenprocoumon permanently, with a target INR of 2.5-3.5 for aortic and 3.0-4.0 for mitral valve prostheses. Direct current (DC) shock cardioversion of early recurrent AF was performed if the patient was symptomatic or hemodynamically compromised. Perioperatively, either the patient's preoperative medication (beta-blocker) was continued or anti-arrhythmic treatment with class III anti-arrhythmic agents (sotalol or amiodarone) was initiated. The therapeutic decision was left to the discretion of the surgeon. After discharge, each patient's anticoagulation and anti-arrhythmic therapy was managed by their general physician or cardiologist.

Follow up

Prospective follow up (FU) examinations were conducted after three, six and 12 months, and annually thereafter. At FU, patients were interviewed and underwent a clinical examination, electrocardiography and transthoracic echocardiography (TTE). Only six patients (4.8%) were unable to visit the clinic; in these cases, interviews were conducted by telephone and the echocardiographic data obtained from the referring cardiologist. Any regular atrial-driven rhythm, including atrial (n = 1), atrioventricular (n = 2), or atrial-triggered ventricular (n = 2) pacing, was regarded as SR.

Echocardiography

Preoperatively, before discharge and at FU, all patients underwent TTE (HP Sonos 5500; Hewlett Packard, Andover, MA, USA). The left atrial (LA) and left ventricular (LV) diameters were measured using standard techniques, and the left ventricular ejection fraction (LVEF) was assessed using the Simpson method. The largest LA area during ventricular systole (systolic LA area) was determined in the apical four-chamber view. In order to assess LA function, the pulsed-wave signal of diastolic transmitral flow was used. Maximal flow velocities of the E and A waves were measured and the E/A ratio was calculated.

Statistical analysis

Unless otherwise indicated, data were presented as mean ± SD, or as absolute and relative frequencies. For comparison of FU and preoperative data within groups, the paired, two-tailed Student's *t*-test was applied. A p-value <0.05 was considered to be statistically significant. Univariate analyses were initially performed to identify risk factors associated with SR

Table II: Patient baseline characteristics.

Parameter	MVD (n = 64)	AVD (n = 37)	CVD (n = 23)
Age (years)+	66 ± 8.6	74 ± 7.8*	70 ± 9.3
Gender			
Female (n)	34 (53.1)	21 (56.8)	10 (43.5)
Male (n)	30 (46.9)	16 (43.2)	13 (56.5)
BSA (m^2)+	1.8 ± 0.19	1.8 ± 0.23	1.9 ± 0.22
NYHA class+	3.0 ± 0.71	3.2 ± 0.72	3.5 ± 0.58**
AF duration (months)+	52 ± 63.7	61 ± 56.4	55 ± 61.3
LA diameter (mm)+	53 ± 8.0	48 ± 5.7**	54 ± 9.6
LA systolic area (cm^2)+	31 ± 8.4	23 ± 5.1**	33 ± 10.2
LVEF (%)+	51 ± 11.5	51 ± 13.1	50 ± 15.1
LVEDD (mm)+	55 ± 8.1	50 ± 8.4†	55 ± 10.0
Logistic EuroSCORE+	9.4 ± 11.28	10.3 ± 8.60	11.3 ± 9.16

Values in parentheses are percentages.
+Values are mean ± SD.
*p <0.001 versus MVD; **p <0.05 versus MVD; †p = 0.049 versus MVD.
AF: Atrial fibrillation; AVD: Aortic valve disease; BSA: Body surface area; CVD: Combined valve disease; LA: Left atrial; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; MVD: Mitral valve disease.

conversion at FU using the unpaired, two-tailed Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Risk factors with a p-value <0.05 on univariate analyses were entered in the multivariate analyses to identify independent risk factors. Their significance for prediction of SR conversion was examined by binary logistic regression analysis. The odds ratio (OR), 95% confidence intervals (CI), and p-values were calculated for each risk factor. The predictive performance of the risk model was assessed by determining the area under the receiver-operating characteristic (ROC) curve; an area of 1.0 was considered to equate to a predictive power of 100%. An arbitrary distribution of the predicted variables in both groups would produce a diagonal in the diagram, resulting in an area under the ROC curve of 0.5. The Hosmer-Lemeshow goodness-of-fit test was performed to evaluate how well the model was calibrated. A small χ^2 value and a p-value >0.05 showed acceptable adaptation. All statistical analyses were performed using a statistical software program (SPSS 13.0 for Windows; SPSS Inc., Chicago, IL, USA).

Results

Patient groups

Gender distribution and global LV function were comparable between the groups (Table II). In general, AVD patients were older and reported a somewhat longer (p = NS) duration of AF. Left atrial dilatation was less pronounced in AVD patients, while CVD patients had a worse NYHA functional status. An increase in the logistic EuroSCORE was also observed in the AVD and CVD groups, although this trend did not reach statistical significance.

Perioperative course

Operative and perioperative data are listed in Table

Table III: Operative and perioperative data.

Parameter	MVD (n = 64)	AVD (n = 37)	CVD (n = 23)
Operation time (min)+	186 ± 37.8	210 ± 53.0	271 ± 75.8*
Aortic cross-clamp time (min)+	76 ± 17.8	101 ± 33.3*	117 ± 34.3*
Ablation time (min)+	11 ± 1.5	11 ± 2.4	11 ± 1.7
Ablation technology			
Microwave (n)	39 (60.9)	23 (62.2)	15 (65.2)
Radiofrequency (n)	25 (39.1)	14 (37.8)	8 (34.8)
Re-exploration for bleeding (n)	1 (1.6)	2 (5.4)	1 (4.3)
Pericardial effusion (n)	1 (1.6)	-	2 (8.7)
Heart failure (n)	6 (9.4)	2 (5.4)	5 (21.7)
IABP (n)	3 (4.7)	-	1 (4.3)
LVAD (n)	1 (1.6)	-	1 (4.3)
Pulmonary failure (n)	1 (1.6)	2 (5.4)	2 (8.7)
Renal failure (n)	2 (3.2)	5 (13.5)	5 (21.7)**
Liver failure (n)	1 (1.6)	-	-
Ischemic events (n)	2 (3.2)	3 (8.1)	2 (8.7)
Transient CVA (n)	2 (3.2)	-	1 (4.3)
Permanent CVA (n)	-	1 (2.7)	1 (4.3)
Others (n)	-	2 (5.4)	-
Intracerebral hemorrhage (n)	1 (1.6)	-	-
Infection (n)	2 (3.2)	3 (8.1)	2 (8.7)
Mediastinitis (n)	-	1 (2.7)	-
Bronchopulmonary infection (n)	2 (3.2)	2 (5.4)	2 (8.7)
Sepsis (n)	-	2 (5.4)	2 (8.7)
DC shock cardioversion (n)	2 (3.2)	4 (10.8)	1 (4.3)
Pacemaker implantation (n)	2 (3.2)	2 (5.4)	2 (8.7)
Hospital stay (days)+	11 ± 11.3	14 ± 9.6	19 ± 19.6
Mortality (30-day) (n)	3 (4.7)	3 (8.1)	2 (8.7)

Values in parentheses are percentages.
+Values are mean ± SD.
*p <0.001 versus to MVD, **p = 0.022.
CVA: Cerebrovascular accident; DC: Direct current; IABP: Intra-aortic balloon pump; LVAD: Left ventricular assist device.
Other abbreviations as Table II.

Table IV: Rhythm outcome at follow up and atrial transport function in sinus rhythm.

Parameter	MVD (n = 56)	AVD (n = 30)	CVD (n = 17)
Sinus rhythm (n)	43 (76.8)	19 (63.3)	10 (58.8)
Missing atrial contraction (n)†	5 (13.2)	-	4 (50.0)
Atrial contraction (n)†	33 (86.8)	18 (100)	4 (50.0)
E/A ratio+	2.5 ± 0.16	2.5 ± 0.13	2.5 ± 0.14
Atrial fibrillation (n)	9 (16.1)	9 (30.0)	6 (35.3)
Atrial flutter (n)	3 (5.4)	1 (3.3)	1 (5.9)

Values in parentheses are percentages.
+Values are mean ± SD.
†Assessment of LA function by pulsed-wave Doppler failed in five, one, and two MVD, AVD, and CVD patients, respectively.
E/A ratio: Ratio of maximal flow velocities of early (E) and atrial (A) diastolic transmitral flow signal assessed by pulsed-wave Doppler. Other abbreviations as Table II.

III. Microwave ablation was used in 61-65% of patients, and cooled-tip RF ablation in 35-39% (p = NS). Due to the complexity of surgery, the aortic cross-clamp time was longer in the AVD and CVD groups. The ablation procedure per se did not cause any injury or death. Class III anti-arrhythmic drugs were administered to 53.1, 51.3 and 43.5% of the MVD, AVD, and CVD patients, respectively (p = NS). Except for a higher incidence of renal failure in CVD patients, perioperative morbidity was similar between groups. Overall, seven patients presented ischemic events, predominantly as regional malperfusion: two strokes (on postoperative day (POD) 1 and 5), three transient neurological deficits (on POD 2, 3 and 6), and one mesenteric infarction (on POD 6); multiple thromboembolism due to hereditary thrombotic thrombocytopenic purpura occurred in one patient on POD 5. Among the AVD and CVD patients there was a trend to prolonged hospital stay (p = NS). Among the MVD, AVD and CVD groups, three (4.7%), three (8.1%) and two (8.7%) patients, respectively, died within 30 days after surgery; thus, the overall perioperative mortality rate was 6.4%. The causes of death were cardiac failure (n = 3), multiple thromboembolic infarctions (n = 1), liver failure (n = 1), and septic multiple organ failure (n = 3; two due to pneumonia and one to mediastinitis).

Follow up

The last available FU data were used for between-group comparisons; the mean FU periods were 10 ± 4.0, 9 ± 4.2 and 10 ± 3.9 months (p = NS) in the MVD, AVD and CVD groups, respectively. Overall, the FU was 97% complete. In total, three patients (one MVD, two AVD) were lost to FU. During the FU period, four (6.6%), two (5.9%) and four (19.0%) patients, respectively, of the MVD, AVD and CVD groups died; thus, the overall mortality rate was 8.6%. The causes of death were heart failure (n = 3), sudden cardiac death (n = 1), multiple organ failure following major abdominal surgery (n = 3), intracerebral hemorrhage (n = 1), rupture of a descending aortic aneurysm (n = 1), and unknown (n = 1).

Results regarding heart rhythm and mechanical LA function are listed in Table IV. All patients in SR has ceased anti-arrhythmia treatment. The assessment of LA function by pulsed-wave Doppler failed in eight patients (Table IV). According to the LVEF, left ventricular function was neither different from preoperative data (Table II) nor between groups (MVD, 51 ± 12.2%; AVD, 53 ± 11.3%; CVD, 52 ± 13.1%; p = NS). Compared to baseline, NYHA functional status improved significantly (p <0.001 in each group) by approximately one class (MVD, 1.9 ± 0.57; AVD, 2.2 ± 0.58; CVD, 2.0 ± 0.42). However, the improvement was somewhat inferior among AVD patients than MVD patients (p <0.05).

Compared to discharge, there was a weak trend towards a higher SR conversion rate after six and 12 months (Fig. 1), though statistical significance was not reached between cohorts, nor at different FU visits.

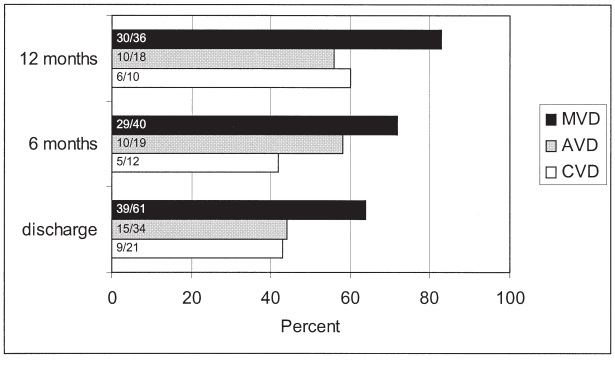

Figure 1: Sinus rhythm (SR) at follow up. The values shown within the bars indicate absolute frequencies of patients in SR.

Table V: Outcome of patients with sinus rhythm.

Outcome	MVD			AVD			CVD		
	SR (n = 43)	Non-SR (n = 13)	p-value	SR (n = 19)	Non-SR (n = 11)	p-value	SR (n = 10)	Non-SR (n = 7)	p-value
NYHA class	1.8 ± 0.62	2.1 ± 0.29	0.078	2.1 ± 0.58	2.4 ± 0.52	NS	2.0 ± 0.50	2.1 ± 0.38	NS
LVEF (%)	51 ± 11.8	53 ± 14.2	NS	54 ± 8.2	53 ± 11.1	NS	55 ± 9.2	48 ± 18.0	NS
LA diameter (mm)	43 ± 6.0*	44 ± 7.2	NS	40 ± 5.4**	46 ± 6.7	<0.05	42 ± 7.8**	52 ± 10.9	0.079
LA systolic area (cm^2)	26 ± 6.1**	30 ± 6.7	0.097	25 ± 4.2	28 ± 4.1	0.083	24 ± 4.3***	27 ± 5.3	NS

*p <0.001; **p <0.05; ***p = 0.058, all versus baseline data.
NS: Not significant; Non-SR: Non-sinus rhythm; SR: Sinus rhythm. Other abbreviations as Table II.

Comparison of patients in SR and non-SR

With regards to LA size, a reversal of atrial remodeling was seen in patients with SR, especially when compared to baseline data (Table V). There was a non-significant trend towards an improved NYHA class with SR. Investigation of the relationship between rhythm outcome and preoperative variables in univariate analysis (Table VI) showed that successful SR conversion was associated with a shorter AF duration and a smaller LA size. Multivariate analysis revealed AF duration (OR 1.01, 95% CI 1.00-1.02, p <0.05) and LA diameter (OR 1.08, 95% CI 1.01-1.15, p <0.05) to be independent risk factors for AF persistence. The predictive performance of the risk model assessed with the area under the ROC curve (Fig. 2; AUC 0.77, 95% CI 0.66-0.88, p <0.001) was sufficient. A model calibration evaluated with the Hosmer-Lemeshow goodness-of-fit test (χ^2 5.6, p = 0.69) showed an acceptable adaptation. A preoperative AF duration of 24 months predicted SR conversion, with a sensitivity of 80% and a specificity of 54% (Fig. 2). Among all patients with less than two years' duration of pAF, 86% were in sinus rhythm at FU (p <0.05).

Discussion

Atrial fibrillation frequently accompanies structural heart disease, and occurs in up to 50% of patients with mitral valve disease, ultimately necessitating cardiac surgery (3,4). AF is also a significant problem in patients undergoing surgery for non-mitral valvular heart disease, as (i) the incidence of AF increases with age, and (ii) the age of patients undergoing cardiac surgery is continuously rising (20,21).

In the present study, the question was raised as to whether SR conversion by LA ablation for AF treatment concomitant with valvular heart surgery depended on the type of underlying heart valve disease. Such a relationship could be assumed; for example in MVD, the left atrial hemodynamic load plays a specific role in initiating and perpetuating the arrhythmia. In accordance with previous reports (13,14), the highest SR restoration rate was observed after AF ablation in mitral valve-related surgery (Table IV; Fig. 1). Among the present patients, however, univariate analysis ruled out a certain type of valvular disease as a determinant of rhythm outcome. This missing association might

Table VI: Univariate analysis of preoperative variables for rhythm outcome.

Parameter	SR (n = 72)	Non-SR (n = 31)	p-value
Age (years)+	68 ± 9.9	69 ± 6.7	NS
Disease			
MVD (n)	43 (59.7)	13 (41.9)	NS
AVD (n)	19 (26.4)	11 (35.5)	NS
CVD (n)	10 (13.9)	7 (22.6)	NS
AF duration (months)+	42 ± 49.0	85 ± 67.2	<0.05
LA diameter (mm)+	50 ± 8.1	55 ± 9.2	<0.05
LA systolic area (cm^2)+	29 ± 8.5	33 ± 10.7	NS
LVEF (%)+	52 ± 12.1	51 ± 11.3	NS
Logistic EuroSCORE+	8.8 ± 9.11	8.9 ± 8.37	NS

Values in parentheses are percentages.
+Values are mean ± SD.
Non-SR: Non-sinus rhythm; NS: Not significant; SR: Sinus rhythm. Other abbreviations as Table II.

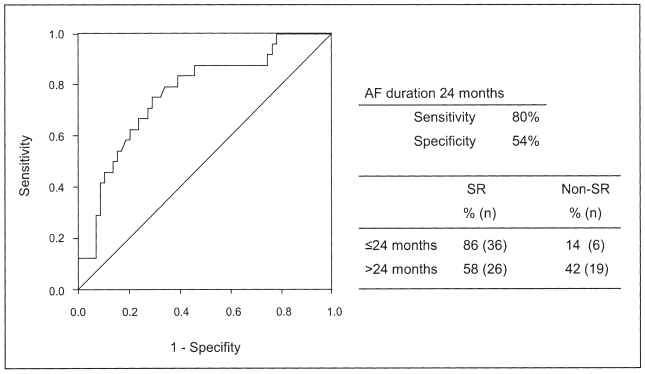

Figure 2: Assessment of the risk model. Left: ROC curve of the risk model predicting sinus rhythm (SR) conversion based on AF duration and LA diameter. The predictive performance assessed with the area under the ROC curve (AUC 0.77, 95% CI 0.66-0.88, p <0.001) and the calibration of the model evaluated with the Hosmer-Lemeshow goodness-of-fit test (χ^2 5.6, p = 0.69) were acceptable. Right: Sensitivity and specificity of a cut-off value of 24 months' AF duration. This value discriminates the observed SR conversion rate (≤24 months, 86%; >24 months, 58%) significantly (p <0.05).

explain why others have reported that AF ablation in patients undergoing aortic valve replacement or coronary artery bypass grafting is as effective as in mitral valve patients (5,15). Among the present patients, the preoperative AF duration and LA diameter were found to be the only independent determinants for successful SR conversion. Overall, 86% of the present patients with a pAF duration of two or less years were in SR at FU (Fig. 2). Similarly, the duration of preoperative AF was shown to be one of the most significant predictors of AF recurrence after the Cox maze procedure in general, and in combination with mitral valve surgery (10,11). Recently, the importance of AF duration and LA size for sinus conversion after concomitant mitral valvular surgery and radiofrequency maze procedure was elucidated in detail (12). Indeed, a shorter AF duration (<66 months) and smaller LA size (<56.8 mm anteroposterior diameter) were associated with superior results in terms of freedom from AF at five years of 87.5% and 88.5%, respectively (12).

Patients with SR at FU exhibited a reversal of atrial remodeling (Table V), and most presented with normal atrial function (Table IV). The trend towards an improved NYHA class with SR (Table V) was recently confirmed by others (5). Because the left ventricular function did not differ between patients with SR and non-SR (Table V), these data might suggest that the re-establishment of SR would in fact reduce the 'burden of atrial fibrillation' - at least in terms of shortness of breath.

Study limitations

As a retrospective analysis of prospectively collected data, the present study suffered from general limitations inherent to observational studies in non-randomized patient groups. Using an identical lesion pattern for LA endocardial ablation by all surgeons, the procedure-associated bias was considered negligible. The application of microwave or RF technology was similar in all groups; moreover, it was shown recently that microwave and RF ablation yield similar success rates for AF treatment (22,23). Excluding those patients with paroxysmal AF from the analysis reduced the cohort size; however, by focusing on pAF the strength of the present findings were most likely increased rather than quantitative power lost.

Acknowledgements

The authors thank Ms. Doreen Boettner for her excellent coordination of the patients' follow up.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946-952
2. Chesebro JH, Fuster V, Halperin JL. Atrial fibrillation - risk marker for stroke. N Engl J Med 1990;323:1556-1558
3. Grigioni F, Avierinos JF, Ling LH, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: Determinants and long-term outcome. J Am Coll Cardiol 2002;40:84-92
4. Gillinov AM. Ablation of atrial fibrillation with mitral valve surgery. Curr Opin Cardiol 2005;20:107-114
5. Geidel S, Ostermeyer J, Lass M, et al. Permanent atrial fibrillation ablation surgery in CABG and aortic valve patients is at least as effective as in mitral valve disease. Thorac Cardiovasc Surg 2006;54:91-95
6. Cox JL, Schuessler RB, D'Agostino HJ, Jr., et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569-583
7. Spitzer SG, Richter P, Knaut M, Schüler S. Treatment of atrial fibrillation in open heart surgery. The potential role of microwave energy. Thorac Cardiovasc Surg 1999;47(Suppl.3):374-378
8. Khargi K, Deneke T, Haardt H, et al. Saline-irrigated, cooled-tip radiofrequency ablation is an effective technique to perform the maze procedure: A prospective randomized study. Ann Thorac Surg 2001;72:S1090-S1095
9. Kottkamp H, Hindricks G, Hammel D, et al.

Intraoperative radiofrequency ablation of chronic atrial fibrillation: A left atrial curative approach by elimination of anatomic anchor reentrant circuits. J Cardiovasc Electrophysiol 1999;10:772-780
10. Gaynor SL, Schuessler RB, Bailey MS, et al. Surgical treatment of atrial fibrillation: Predictors of late recurrence. J Thorac Cardiovasc Surg 2005;129:104-111
11. Gillinov AM, Sirak J, Blackstone EH, et al. The Cox maze procedure in mitral valve disease: Predictors of recurrent atrial fibrillation. J Thorac Cardiovasc Surg 2005;130:1653-1660
12. Chen MC, Chang JP, Chang HW, et al. Clinical determinants of sinus conversion by radiofrequency maze procedure for persistent atrial fibrillation in patients undergoing concomitant mitral valvular surgery. Am J Cardiol 2005;96:1553-1557
13. Mohr FW, Fabricius AM, Falk V, et al. Curative treatment of atrial fibrillation with intraoperative radiofrequency ablation. J Thorac Cardiovasc Surg 2002;123:919-927
14. Sie HT, Beukema WP, Elvan A, Misier ARR. Long-term results of irrigated radiofrequency modified maze procedure in 200 patients with concomitant cardiac surgery: Six years experience. Ann Thorac Surg 2004;77:512-517
15. Khargi K, Lemke B, Deneke T. Concomitant antiarrhythmic procedures to treat permanent atrial fibrillation in CABG and AVR patients are as effective as in mitral valve patients. Eur J Cardiothorac Surg 2005;27:841-846
16. Levy S, Camm AJ, Saksena S, et al. International consensus on nomenclature and classification of atrial fibrillation: A collaborative project of the working group on arrhythmias and the working group of cardiac pacing of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. J Cardiovasc Electrophysiol 2003;14:443-445
17. Cox JL. Surgical treatment of atrial fibrillation: A review. Europace 2004;5:S20-S29
18. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9-13
19. Isobe F, Kumano H, Ishikawa T, et al. A new procedure for chronic atrial fibrillation: Bilateral appendage-preserving maze procedure. Ann Thorac Surg 2001;72:1473-1478
20. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. Am J Cardiol 1998;82:2N-9N
21. Kalmar P, Irrgang E. Cardiac surgery in Germany during 2003: A report by the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2004;52:312-317
22. Wisser W, Khazen C, Deviatko E, et al. Microwave and radiofrequency ablation yield similar success rates for treatment of chronic atrial fibrillation. Eur J Cardiothorac Surg 2004;25:1011-1017
23. Topkara VK, Williams MR, Barili F, et al. Radiofrequency and microwave energy sources in surgical ablation of atrial fibrillation: A comparative analysis. Heart Surgery Forum 2006;9:E614-E617

2.2.2. Wiederauftreten von Vorhofflimmern: zeitbestimmende Faktoren

Grubitzsch H, Grabow C, Orawa H, Konertz W.

Factors predicting the time until atrial fibrillation recurrence after concomitant left atrial ablation.

Eur J Cardiothorac Surg. 2008; 34: 67-72.

Zusammenfassung der Ergebnisse

In dieser Studie wurden 162 Patienten (52,5% männlich, Alter 69±8,7 Jahre) mit permanentem Vorhofflimmern untersucht. Alle Patienten wurden einer linksatrialen Ablation und einem isolierten bzw. kombinierten Mitralklappeneingriff (42,6%), einem isolierten bzw. kombiniertem Aortenklappeneingriff (32,1%) oder einer isolierten bzw. kombinierten operativen Koronarrevaskularisation (24,1%) unterzogen. Die Nachuntersuchungen wurden nach 3, 6, 12 Monaten und danach jährlich durchgeführt. Das interessierende Ereignis war persistierendes Vorhofflimmern nach dem operativen Eingriff. Die prädiktiven Werte von Variablen für postoperatives Vorhofflimmern wurden mit Techniken der uni- und multivariaten Überlebensanalyse untersucht. Um die Auswirkungen verschiedener potentieller Risikofaktoren zur selben Zeit zu bestimmen, wurde eine Cox-Regressionsanalyse (proportional hazard regression) durchgeführt. Zur letzten Nachuntersuchung (nach 19±11,3 Monaten) waren 86 Patienten (62%) im stabilen Sinusrhythmus – 73 (52%) ohne Antiarrhythmika – und 43 (31%) im Vorhofflimmern. Prädiktoren für die Zeit bis zum Wiederauftreten von Vorhofflimmern waren im multivariaten Modell die präoperative Dauer des Vorhofflimmerns (hazard ratio [HR] 1,005, 95%-KI 1,003-1,007, $p<0,001$) und der linksatriale Durchmesser (HR 1,056, 95%-KI 1,020-1,093, $p=0,002$). Alter, Geschlecht, die primäre Herzerkrankung, thromboembolische Ereignisse, durchgeführte Kardioversionen, Begleiterkrankungen, EuroSCORE, die linksventrikuläre Größe und Funktion, die Aortenklemmzeit, die Ablationstechnologie und die Behandlung mit Antiarrhythmika bestimmten nicht das Rhythmusergebnis.

Auch für die Zeit bis zum Wiederauftreten von Vorhofflimmern nach begleitender linksatrialer Ablation sind die präoperative Vorhofflimmerdauer und der linksatriale Durchmesser Prädiktoren. Jede Zunahme der Vorhofflimmerdauer um einen Monat korrespondiert mit einer Erhöhung des Risikos für rekurrentes Vorhofflimmern von 0,5%

und jede Zunahme des linksatrialen Durchmessers um einen Millimeter mit einer 5,6%igen Risikoerhöhung.

ELSEVIER

European Journal of Cardio-thoracic Surgery 34 (2008) 67–72

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Factors predicting the time until atrial fibrillation recurrence after concomitant left atrial ablation

Herko Grubitzsch [a,*], Christian Grabow [a], Helmut Orawa [b], Wolfgang Konertz [a]

[a] Department of Cardiovascular Surgery, Charité — Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany
[b] Department of Biostatistics and Clinical Epidemiology, Charité — Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany

Received 1 December 2007; received in revised form 29 March 2008; accepted 31 March 2008; Available online 23 May 2008

Abstract

Objective: Treatment of atrial fibrillation, a risk factor for morbidity and mortality, by left atrial ablation is a less complex procedure which is increasingly performed in conjunction with surgery for various heart diseases. Although restoration of sinus rhythm is effective initially, atrial fibrillation may recur. We investigated factors predicting the time until its recurrence. **Methods:** Between January 2003 and December 2005, 162 consecutive patients (52.5% male, age 69 ± 8.7 years) with permanent atrial fibrillation underwent concomitant left atrial ablation and isolated or combined mitral valve surgery (42.6%), isolated or combined aortic valve surgery (32.1%), and isolated or combined coronary artery bypass grafting (24.1%). Ablation was performed by microwave (n = 93, 57.4%) or radiofrequency (n = 69, 42.6%) technology. Follow-up was after 3, 6, 12 months and yearly thereafter. Predictive values of variables for postoperative atrial fibrillation were examined using techniques of univariate and multivariate survival analysis (proportional hazards regression). **Results:** Eight patients died perioperatively and 13 during follow-up (not ablation related). Two patients were lost to follow-up. At last follow-up (19 ± 11.3 months), 86 patients (62%) were in stable sinus rhythm, 73 (52%) without antiarrhythmic drugs, and 43 (31%) were in atrial fibrillation. Predictors for the time until recurrence of atrial fibrillation in a multivariate model were preoperative atrial fibrillation duration (hazard ratio 1.005, 95% confidence interval 1.003–1.007, $p < 0.001$) and left atrial diameter (hazard ratio 1.056, 95% confidence interval 1.020–1.093, p = 0.002). Overall, sinus rhythm conversion rate was 75% when preoperative atrial fibrillation duration was less than 2 years, but 42% in longer lasting atrial fibrillation with left atrial dilatation (>50 mm). Age, gender, primary heart disease, history of thromboembolism or cardioversion, presence of concomitant diseases, EuroScore, left ventricular size and function, aortic cross-clamp time, ablation technology, and treatment with antiarrhythmic drugs did not predict rhythm outcome. **Conclusions:** Preoperative atrial fibrillation duration and left atrial diameter predict the time until atrial fibrillation recurrence after concomitant left atrial ablation, whereas age, type of primary cardiac surgery, ablation technology and antiarrhythmic therapy do not.

Keywords: Atrial fibrillation; Ablative therapy; Valvular surgery; Coronary artery bypass grafting

1. Introduction

Atrial fibrillation (AF) is an arrhythmia that is associated with an increased risk of stroke and premature death [1,2]. Overall, AF incidence increases with age [3] and frequently, AF accompanies structural heart disease. Thus, a significant number of patients referred for cardiac surgery present with AF.

In recent years, surgical AF treatment, classically performed as cut-and-sew maze operation [4], has developed to a less complex procedure by using different energy sources for tissue ablation. Nowadays, ablation is increasingly focused on the left side, because it became clear that AF would not recur if macro re-entry can be prevented by lesions critically placed in the left atrium [5–7]. In fact, this approach allows treatment of AF in combination with surgical interventions for almost all heart diseases.

Although restoration of SR is achieved in the majority of patients, identification of factors determining AF persistence or recurrence may further improve results. So far, for AF treatment mostly in combination with mitral valve surgery (cut-and-sew maze, radiofrequency maze, left atrial ablation), preoperative AF duration, left atrial size, age, rheumatic mitral valve disease, left ventricular ejection fraction (LVEF), and lesion pattern have been described as factors of AF recurrence [8–14].

Our objective was to assess left atrial ablation for treatment of permanent AF routinely performed in all types of cardiac surgery. We focussed on factors predicting the time until AF recurs.

* Corresponding author. Address: Klinik für Kardiovaskuläre Chirurgie, Charité — Universitätsmedizin Berlin, Campus Charité Mitte, Charité-Platz 1, 10117 Berlin, Germany. Tel.: +49 30 450522092; fax: +49 30 450522921.
E-mail address: herko.grubitzsch@charite.de (H. Grubitzsch).

1010-7940/$ — see front matter
doi:10.1016/j.ejcts.2008.03.054

2. Materials and methods

2.1. Patients

Between January 2003 and December 2005, a total of 162 consecutive patients (52.5% male) underwent concomitant AF ablation. Their mean age was 69 ± 8.7 years. According to established definitions [6,15], all patients presented with permanent/continuous AF. The median of AF duration was 24 months (interquartile range 6.25—72.0 months). Preoperative diameter of the left atrium was 50 ± 8.2 mm (median 50 mm). After obtaining approval of the local ethics committee and individual informed consent for the study, preoperative, perioperative and follow-up data were prospectively entered into an institutional database.

2.2. Surgical procedure

Procedures for primary cardiac surgery are listed in Table 1. For all procedures, standard normothermic cardiopulmonary bypass and warm antegrade blood cardioplegia were used. All patients underwent endocardial AF ablation by a strict left atrial approach. According to device's availability, the lesion set (Fig. 1) was created using microwave (Flex 4®, Guidant Corporation, Santa Clara, CA, USA) or radiofrequency (Cardioblate®, Medtronic Incorporation, Minneapolis, MN, USA) technology in 93 (57.4%) and 69 (42.6%) cases, respectively. The left atrial appendage was oversewn only if thrombi were inside (n = 3). The transthoracic echocardiographic examination (TEE) probe was removed during ablation to avoid esophageal injury.

2.3. Perioperative treatment

All patients were anticoagulated with heparin followed by phenprocoumon. After 3 months and stable sinus or atrial driven pacemaker rhythm in Holter ECG and mechanical atrial function in echocardiogram, anticoagulation was stopped. Patients with mechanical valve substitutes were kept on phenprocoumon permanently. DC shock cardioversion of early recurrent AF was performed if patient was symptomatic or hemodynamically compromised. At the discretion of the surgeon, either patient's preoperative medication was continued or antiarrhythmic treatment with class III antiarrhythmic drugs (sotalol or amiodarone) was initiated. After discharge, patient's general practitioner or cardiologist managed the anticoagulation and antiarrhythmic therapy.

Table 1
Surgical procedures

	n	(%)
MVP/-R	69	42.6
Isolated	43	26.6
+TVP/R/+CABG/+congenital	26	16.1
AVR	52	32.1
Isolated	32	19.8
+MVP/-R/+TVP/−R/+CABG/+AAR	20	12.3
CABG	39	24.1
Isolated	38	23.5
+Aneurysmectomy	1	0.6
Other procedures	2	1.2
Reoperation	10	6.2

MVP, mitral valve plasty; MVR, mitral valve replacement; TVP, tricuspid valve plasty; TVR, tricuspid valve replacement; CABG, coronary artery bypass grafting; AAR, ascending aortic replacement; AVR, aortic valve replacement.

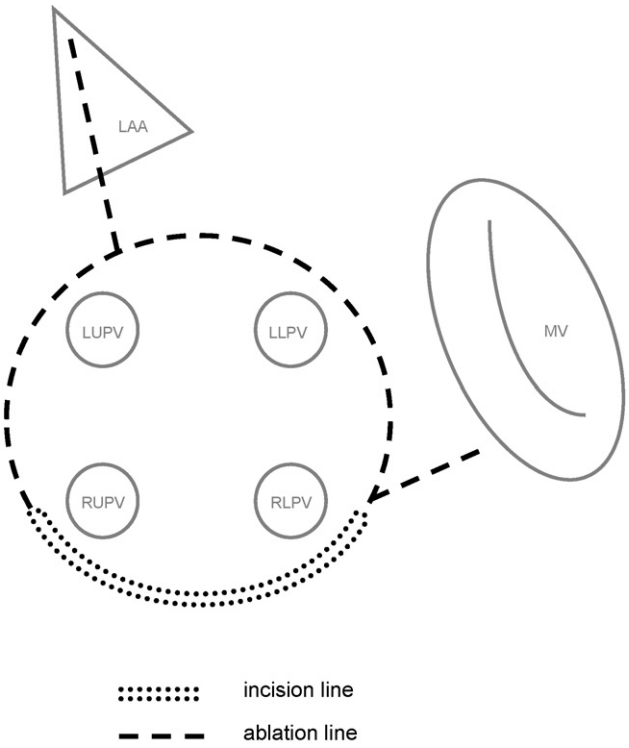

Fig. 1. Lesion set. The lesion pattern consisted of (I) left atrial posterior wall ablation isolating all pulmonary vein ostia, (II) a line into the left atrial appendage, and (III) a line to the mitral valve annulus (P3).

2.4. Follow-up

After 3, 6, 12 months and annually thereafter, patients were interviewed and underwent clinical, electrocardiographic and transthoracic echocardiographic examination. At 3 and 12 months, heart rhythm was monitored by 24 h Holter ECG. In only seven patients (4.3%), who were not able to visit the clinic, interviewing was done by telephone and ECG and echocardiographic data were obtained from the referring cardiologist. Any regular atrial driven rhythm, including atrial (n = 2), atrioventricular (n = 2), or atrial triggered ventricular (n = 4) pacing, was regarded as sinus rhythm (SR).

2.5. Echocardiography

Preoperatively, before discharge and at follow-up, all patients underwent TTE using the HP Sonos 5500 (Hewlett Packard, Andover, Massachusetts, USA). Left atrial and left ventricular diameters were measured using standard techniques. Left ventricular ejection fraction (LVEF) was assessed by the Simpson method. For assessment of left atrial function the pulsed-wave signal of diastolic transmitral flow was used. Maximal flow velocities of early (E) and atrial (A) waves were measured and E/A ratio was calculated.

2.6. Statistical analysis

Overall rhythm outcome was assessed as AF prevalence at each follow-up visit. AF-free intervals were analyzed according to the Kaplan—Meier (K—M) method (definitions see below). The interesting event was persistent AF after surgery, defined as documented AF (ECG) in two sequential follow up visits. The middle of the period between last visit in SR and first visit in AF was assumed as time of occurrence. Data from patients with SR were censored at the time of last follow-up. Patients who died ($n = 21$), and patients who were lost to follow up ($n = 2$) were censored, too. Patients presenting with heart rhythm other than AF or SR ($n = 3$) and patients repeatedly alternating between SR and AF ($n = 7$) were excluded from analysis. Since the results of the rhythm examination are grouped into time intervals, the K—M method is as precise as the actuarial method. In order to detect potential risk factors predicting the time until AF recurrence, first durations of freedom from AF of several subgroups of patients were compared using the log-rank test. The fact that the subgroups were samples from the same population regarding freedom from AF was tested as null hypothesis. In order to explore the effects of several potential risk factors at the same time, a second Cox (proportional hazards) regression analysis was performed. The hazard ratio (HR) and 95% confidence interval (CI) of the HR were calculated for each predictor. Trying to obtain the model that predicts the time to AF recurrence best, forward and backward stepwise regression was carried out The cut-off level for statistical significance was taken at 0.05. The distribution of continuous variables in patient groups, was compared using Mann—Whitney's *U*-test. The distribution of categorical variables was contrasted using the χ^2-test or Fisher's exact test. Analysis was performed using a statistical program (SPSS 13.0 for Windows, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Procedural outcome

Ablation time, aortic cross-clamp time, cardiopulmonary bypass time, and operation time were 11 ± 1.9 min, 84 ± 30.0 min, 116 ± 35.9 min, and 209 ± 50.3 min, respectively. Patients were discharged from hospital after 16 ± 14.0 days. Perioperative morbidity was characterized by re-exploration for bleeding ($n = 5$), late pericardial effusion ($n = 3$), heart failure ($n = 7$) requiring intra-aortic balloon pump support ($n = 6$) and temporary left ventricular assist device placement ($n = 1$), renal failure ($n = 20$), pneumonia ($n = 13$), mediastinitis ($n = 1$), and cerebrovascular accident ($n = 5$). Perioperative mortality (30 days) was 4.9% due to cardiac failure ($n = 2$), septic multiple organ failure ($n = 5$), and rupture of a descending aortic aneurysm ($n = 1$). Ablation procedure per se did not cause any injury or death.

The last available follow-up visit was after 19 ± 11.2 months. In total, two patients (1.2%) were lost and 13 patients (8.0%) died during follow-up. Causes of death were heart failure ($n = 4$), sudden cardiac death ($n = 1$), multiple organ failure following major abdominal surgery ($n = 2$), pneumonia ($n = 2$), intracerebral hemorrhage ($n = 1$), and unknown ($n = 3$). Thromboembolic events did not occur.

From 139 patients available for follow-up, 86 (62%) were in stable sinus rhythm, 73 (52%) without antiarrhythmic drugs, and 43 (31%) were in AF at last visit. Remaining patients were alternating between SR and AF ($n = 7$), presented atrial flutter ($n = 2$) or AV junctional rhythm ($n = 1$). AF prevalence at each follow-up visit and the Kaplan—Meier estimates of overall freedom from AF over time are shown in Fig. 2.

3.2. Predictors for AF recurrence

Table 2 lists preoperative and perioperative characteristics that were analyzed as potential factors for rhythm outcome. Age, gender, body surface area, history of thromboembolism or cardioversion, NYHA functional class, left ventricular size and function, primary heart disease, presence of concomitant diseases, EuroScore, ablation time and technology, and perioperative treatment with antiarrhythmic drugs or DC shock cardioversion did not determine AF recurrence.

The final proportional hazard regression model contains two explanatory variables: preoperative AF duration (hazard ratio [HR] 1.005, 95% confidence interval [CI] 1.003—1.007, $p < 0.001$) and preoperative LA size (HR 1.056, 95% CI 1.020—

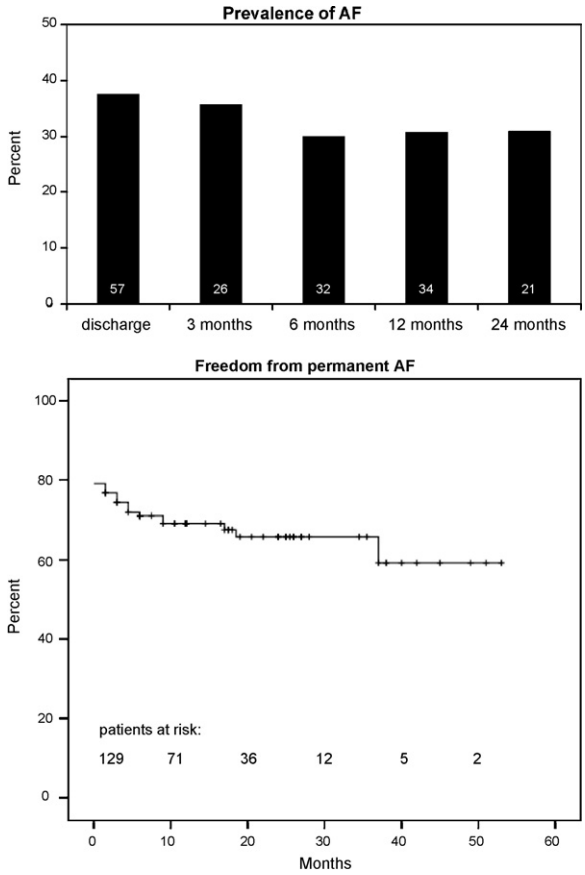

Fig. 2. Atrial fibrillation after ablation. The upper graph shows AF prevalence at certain follow-up visits. The lower graph depicts Kaplan—Meier estimates of freedom from AF. Numbers in bars reflect absolute frequency of patients presenting with AF.

Table 2
Factors for AF recurrence

	Hazard ratio	95% Confidence interval	*p*-Value
Age (years)	1.027	0.991—1.065	0.146
Gender (female/male)	0.858	0.471—1.566	0.618
Body surface area (m^2)	1.737	0.464—6.461	0.414
AF duration (months)	1.004	1.002—1.007	<0.001
Previous thromboembolism (yes/no)	0.631	0.248—1.600	0.327
Previous DC shock cardioversion (yes/no)	1.566	0.379—6.472	0.532
NYHA class (I—II/III—IV)	1.011	0.519—1.969	0.974
LA diameter (mm)	1.039	1.005—1.075	0.026
LVEF (%)	1.009	0.983—1.034	0.509
LVEDD (mm)	1.017	0.972—1.064	0.473
Mitral valve disease (yes/no)	0.810	0.512—1.688	0.810
Aortic valve disease (yes/no)	1.266	0.650—2.315	0.528
Coronary artery disease (yes/no)	0.864	0.478—1.560	0.627
Extracardiac artery disease (yes/no)	1.400	0.551—3.557	0.477
Arterial hypertension (yes/no)	0.859	0.442—1.667	0.652
Pulmonary hypertension (yes/no)	1.728	0.889—3.358	0.103
Chronic obstructive lung disease (yes/no)	1.200	0.577—2.497	0.626
Renal dysfunction (yes/no)	0.904	0.420—1.945	0.796
Diabetes mellitus (yes/no)	1.29	0.697—2.385	0.416
Logistic EuroScore (%)	1.004	0.970—1.039	0.812
Aortic cross-clamp time (min)	0.993	0.981—1.006	0.293
Ablation time (min)	1.027	0.966—1.093	0.389
Ablation technology (RF/MW)	1.080	0.080—6.433	0.299
Class III antiarrhythmic drugs (postoperative) (yes/no)	1.729	0.680—4.392	0.244
DC shock cardioversion (postoperative) (yes/no)	0.840	0.260—2.715	0.771

AF, atrial fibrillation; DC, direct current; NYHA, New York Heart Association; LA, left atrial; LVEF, left ventricular ejection fraction, LVEDD, left ventricular end diastolic diameter; RF, radiofrequency; MW, microwave.

1.093, $p = 0.002$) are the best predictors of the time until AF recurrence after operation. Taking the median of AF duration and LA diameter of our cohort as cut-off values, Fig. 3 shows that sinus rhythm conversion rate was superior when preoperative AF duration was 2 years or less. In longer lasting AF, LA dilatation worsened the results if LA diameter was larger than 50 mm.

3.3. Follow-up results according to heart rhythm

According to transmitral diastolic flow-pattern, 91.1% of patients with SR at latest follow-up presented with normal atrial transport function with an E/A ratio of 2.4 ± 0.82. Compared to patients with AF, more patients with successful SR conversion were in a NYHA class II or less (75 [87.1%] vs 33 [76.7%] patients, $p = 0.023$). Based on the number of patients reporting palpitations there was a non-significant trend to fewer episodes with SR (3 [3.5%] vs 5 [11.6%] patients, $p = 0.173$). Although left atrial diameter was significantly smaller in SR patients (40 ± 6.8 vs 44 ± 7.1 mm, $p = 0.002$), the magnitude of size reduction after operation was comparable in each group (23 ± 12.1 vs 19 ± 11.9%, $p = 0.134$). There was no significant difference in dimensions or function of the left ventricle. In patients with AF versus SR, treatment with beta-blocker (32 [74.4%] vs 72 patients [83.7%], $p = 0.376$) and class III antiarrhythmic drugs (3 [7.0%] vs 11 patients [12.8%], $p = 0.346$) was similar, whereas digitalis was taken more frequently (16 [37.2%] vs 14 patients [16.3%], $p = 0.006$). The majority of AF patients ($n = 38$, 88.4%) were treated with anticoagulants. However, 37 SR patients (43.0%) were still on phenprocoumon.

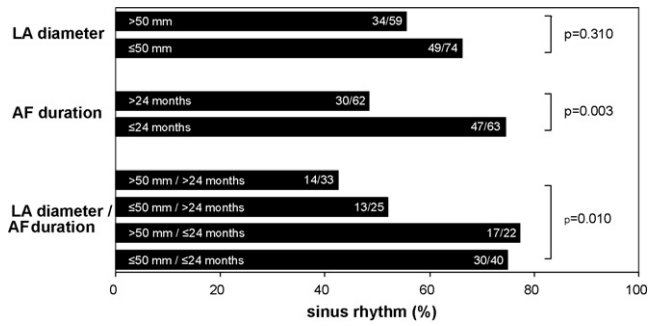

Fig. 3. Relationship between predictors of time to AF recurrence and presence of sinus rhythm at last follow-up. According to the median of preoperative LA diameter and AF duration, several patient groups were created (see left-sided legend within bars). Observed sinus rhythm restoration rate at last follow-up is shown. Right-sided numbers within bars reflect absolute frequencies of patients with sinus rhythm. For comparison the χ^2-test was used.

4. Discussion

With this study we evaluated factors predicting the time until AF recurrence after concomitant left atrial ablation for treatment of permanent AF in patients undergoing cardiac surgery for coronary artery, valvular, or combined heart disease. Out of a huge variety of potential factors examined, only preoperative AF duration and left atrial size were significant determinants for rhythm outcome. Every 1-month increase in AF duration corresponded to an increase in the risk for recurrent AF after surgery of 0.5% and every 1 mm increase in left atrial diameter to a 5.6%-increase in the risk.

Whereas with biatrial maze procedures, performed using either the cut-and-sew technique or ablative technology,

Table 3
Factors found predictive for AF recurrence after surgical AF treatment

	Biatrial procedure (Cox-maze)		Left atrial ablation
	Cut-and-sew technique	Alternative energy sources	
AF duration	• [8,9]	• [11]	
LA diameter	• [8,10]	• [11,12]	
Age	• [8]		• [13]
Rheumatic MV disease		• [12]	• [14]
Previous MV procedure			• [14]
Lesion pattern			• [13]
LVEF			• [14]
LV mass index	• [8]		
Magnitude of atrial fibrillatory wave	• [10]		
AF presence at discharge			• [13]

AF, atrial fibrillation; LA, left atrial; MV, mitral valve; LVEF, left ventricular ejection fraction; LV, left ventricular.

preoperative AF duration and left atrial size have been reported to be the most important predictors for AF recurrence [8—11], this has not been demonstrated with left atrial ablation so far (Table 3) [13,14]. A reason could be that only 67% and 73% of patients from the left atrial ablation studies presented with permanent AF that may have outweighed the influence of AF duration or LA size. Furthermore, Manasse et al. [13] used several different lesion patterns that determined the results rather than did the AF criteria. The importance of left atrial lesions including wide pulmonary vein isolation, at least one connection line between the left and right pulmonary veins, and a connection to the mitral valve annulus when applying alternative energy sources has been proved recently [7]. Pulmonary vein isolation and lesion sets that did not include a lesion to the mitral annulus were less effective for the treatment of permanent AF [7].

In our cohort, SR conversion rate was satisfactory in patients with preoperative AF duration of up to two years (Fig. 3). If AF lasted longer, only 48% of patients were in SR at last follow-up. Left atrial dilatation beyond 50 mm in diameter led to a further reduction of the success rate to 42%. Undoubtedly, from our experience we can conclude that concomitant treatment of permanent AF by left atrial ablation should be undertaken early, if possible before preoperative AF duration exceeds two years. It seems reasonable to consider reduction plasty, if the left atrium is dilated more than 50 mm in diameter. Due to the heterogeneity of our cohort, we may have neither been able to define clear cut-off values of AF predictors nor find out if the magnitude of AF duration and left atrial size, which is associated with satisfactory rhythm results, differs between patients with primary mitral valve disease, aortic valve disease or coronary artery disease.

Whether or not patients with longer lasting AF may benefit from concomitant biatrial ablation or a cut-and-sew Cox-maze III procedure remains a matter of debate. Regarding the excellent SR conversion rates after concomitant Cox-maze or similar procedures [8,10,11], the younger mean age in these cohorts (ranging from 51 to 62 years) has to be considered. AF incidence increases with age in general [3] and older age was shown to be a significant patient-related risk factor for postoperative AF [7]. According to Khargi's meta-analysis that investigated cut-and-sew procedures and ablative techniques, the SR conversion rate was similar when both age and frequency of paroxysmal or lone AF were taken into consideration [16]. Another report claims that biatrial approaches were more effective than left atrial ones, but the patients' age was completely ignored in this analysis [17]. The mean age of our patients was almost 70 years and increasing age of patients requiring cardiac surgery has to be anticipated for the future. From that point of view, focusing concomitant AF treatment on the left atrium, where the majority of AF is anchored, could be a reasonable way of reducing operative risk, which is higher in older age [18].

In this and other studies [19,20], a beneficial effect of SR conversion on functional status could be demonstrated. This probably results from restored atrial transport function in the majority of patients with SR, as the left ventricular function was comparable to that of patients developing recurrent AF. Obviously, the frequency of palpitations reported by patients was higher when AF recurred.

4.1. Limitations of the study

We used Holter monitoring data and ECGs at follow-up visits for the assessment of heart rhythm results. Hence, asymptomatic AF episodes occurring meanwhile may have been missed. However, continuous monitoring of heart rhythm is currently not feasible, even with 7 days Holter monitoring or event recorders [21]. Certainly, bias was reduced by excluding patients with repeated alternations between SR and AF from analysis.

As time until recurrence of AF was in focus, we used proportional hazards regression as statistical tool for identifying risk factors. The assumption of proportional hazard functions in patients with permanent AF undergoing concomitant ablation seems reasonable. The fact that postoperative AF prevalence has an early peak component and a chronic constant phase [7] suggests that effects of variables influencing the time until AF recurrence are not constant over time. In general, analysis of AF recurrence using survival data methodology is difficult and interpretation must be done with caution [21]. If continuous monitoring of rhythm and its duration becomes available in the near future, the most appropriate method of reporting rhythm outcome will be time-related burden of AF.

Acknowledgement

We are thankful to Mrs Doreen Boettner for the excellent work she did in co-ordinating patients' follow-up.

References

[1] Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946—52.
[2] Chesebro JH, Fuster V, Halperin JL. Atrial fibrillation — risk marker for stroke. N Engl J Med 1990;323:1556—8.
[3] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N—9N.
[4] Cox JL, Schuessler RB, D'Agostino Jr HJ, Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569—83.
[5] Kottkamp H, Hindricks G, Hammel D, Autschbach R, Mergenthaler J, Borggrefe M, Breithardt G, Mohr FW, Scheld HH. Intraoperative radiofrequency ablation of chronic atrial fibrillation: a left atrial curative approach by elimination of anatomic anchor reentrant circuits. J Cardiovasc Electrophysiol 1999;10:772—80.
[6] Cox JL. Surgical treatment of atrial fibrillation: a review. Europace 2004;5:S20—9.
[7] Gillinov AM, Bhavani S, Blackstone E, Rajeswaran J, Svensson LG, Navia JL, Pettersson BG, Sabik JF, Smedira NG, Mihaljevic T, McCarthy PM, Shewchick J, Natale A. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. Ann Thorac Surg 2006;82:502—14.
[8] Gillinov AM, Sirak J, Blackstone EH, McCarthy PM, Rajeswaran J, Pettersson G, Sabik FJ, Svensson LG, Navia JL, Cosgrove DM, Marrouche N, Natale A. The Cox maze procedure in mitral valve disease: predictors of recurrent atrial fibrillation. J Thorac Cardiovasc Surg 2005;130:1653—60.
[9] Gaynor SL, Schuessler RB, Bailey MS, Ishii Y, Boineau JP, Gleva MJ, Cox JL, Damiano RJ. Surgical treatment of atrial fibrillation: predictors of late recurrence. J Thorac Cardiovasc Surg 2005;129:104—11.
[10] Kamata J, Kawazoe K, Izumoto H, Kitahara H, Shiina Y, Sato Y, Nakai K, Ohkubo T, Tsuji I, Hiramori K. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operations. Ann Thorac Surg 1997;64:394—8.
[11] Chen MC, Chang JP, Chang HW, Chen CJ, Yang CH, Chen YH, Fu M. Clinical determinants of sinus conversion by radiofrequency maze procedure for persistent atrial fibrillation in patients undergoing concomitant mitral valvular surgery. Am J Cardiol 2005;96:1553—7.
[12] Baek MJ, Na CY, Oh SS, Lee CH, Kim JH, Seo HJ, Park SW, Kim WS. Surgical treatment of chronic atrial fibrillation combined with rheumatic mitral valve disease: effects of the cryo-maze procedure and predictors for late recurrence. Eur J Cardiothorac Surg 2006;30:728—36.
[13] Manasse E, Gaita F, Ghiselli S, Barbone A, Garberoglio L, Citterio E, Ornaghi D, Gallotti R. Cryoablation of the left posterior atrial wall: 95 patients and 3 years of mean follow-up. Eur J Cardiothorac Surg 2003;24:731—40.
[14] Fayad G, Le Tourneau T, Modine T, Azzaoui R, Ennezat PV, Decoene C, Deklunder G, Warembourg H. Endocardial radiofrequency ablation during mitral valve surgery: effect on cardiac rhythm, atrial size, and function. Ann Thorac Surg 2005;79:1505—11.
[15] Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith Jr SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol 2006;48:e149—246.
[16] Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. Eur J Cardiothorac Surg 2005;27:258—65.
[17] Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. J Thorac Cardiovasc Surg 2006;131:1029—35.
[18] Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroScore). Eur J Cardiothorac Surg 1999;16:9—13.
[19] Grubitzsch H, Beholz S, Dohmen P, Dushe S, Liu J, Konertz W. Ablation of atrial fibrillation in valvular heart surgery: are results determined by underlying valve disease? J Heart Valve Dis 2007;16:76—83.
[20] Grubitzsch H, Dushe S, Beholz S, Dohmen PM, Konertz W. Surgical ablation of atrial fibrillation in patients with congestive heart failure. J Card Fail 2007;13:509—16.
[21] Shemin RJ, Cox JL, Gillinov AM, Blackstone EH, Bridges CR. Guidelines for reporting data and outcomes for the surgical treatment of atrial fibrillation. Ann Thorac Surg 2007;83:1225—30.

2.3. Die chirurgische Therapie von Vorhofflimmern bei chronischer Herzinsuffizienz

Die Prognose von Patienten mit chronischer Herzinsuffizienz und Vorhofflimmern ist stark eingeschränkt. Da mit den modernen Verfahren der chirurgischen Therapie des Vorhofflimmerns in der Mehrheit der Patienten Sinusrhythmus erreicht wird (siehe 2.1. und 2.2), sollte die begleitende Vorhofablation bei Patienten mit Herzinsuffizienz und Vorhofflimmern, die sich einer herzchirurgischen Operation unterziehen, evaluiert werden.

Grubitzsch H, Dushe S, Beholz S, Dohmen PM, Konertz W.
Surgical ablation of atrial fibrillation in patients with congestive heart failure.
J Card Fail. 2007;13: 509-16.

Zusammenfassung der Ergebnisse

Mit dieser Studie wurden die Ergebnisse nach begleitender Vorhofablation bei Patienten mit Herzinsuffizienz untersucht. Von insgesamt 212 Patienten (Alter 69±8,8 Jahre) mit Vorhofflimmern (87% persistierend), die sich einer zusätzlichen linksatrialen Ablation unterzogen, wiesen 79 (37,3%) eine Herzinsuffizienz (NYHA-Klasse ≥III und LVEF ≤45%) auf. Bei 62 Patienten bestand eine moderate (LVEF 31-45%) und bei 17 Patienten eine schwere linksventrikuläre Dysfunktion (LVEF ≤30%).
Patienten mit Herzinsuffizienz und Kontrollpatienten waren vergleichbar hinsichtlich Dauer des Vorhofflimmerns, Größe des linken Vorhofs, Aortenabklemmzeit, kardiopulmonaler Bypass-Zeit und Operationszeit. In der Herzinsuffizienz-Gruppe bestand ein allgemeiner Trend zu einem erhöhten perioperativen Risiko (Morbidität, Hospitalisierung, Letalität). Nach 13±7,3 Monaten waren 42 Patienten (66%) mit Herzinsuffizienz und 81 Kontroll-Patienten (74%) im Sinusrhythmus (p=0,301); 55% und 64% ohne Antiarrhythmika (p=0,234). Die Sinusrhythmus-Konversion war nicht mit klinischen bzw. echokardiografischen Parametern der Herzinsuffizienz assoziiert. Die Wiederherstellung von Sinusrhythmus ging bei Patienten mit schwerer linksventrikulärer Dysfunktion mit einer deutlichen Verbesserung der NYHA-Klasse (1,6±0,75 versus

2,5±0,81, p=0,005) und des Minnesota-Living-with-Heart-Failure- (MLHF-) Gesamtpunktwertes (19±18,2 versus 45±9,4, p=0,016) einher. Ähnlich wurde die physische Komponente des MLHF-Score bei schwerer Herzinsuffizienz verbessert (9±11,7 versus 26±9,2, p=0,062). Bei Patienten mit moderater linksventrikulärer Dysfunktion führte die Sinusrhythmus-Konversion zu keiner zusätzlichen Verbesserung. Sinusrhythmus beeinflusste weder die emotionale Komponente des MLHF-Score noch die mittels 6-minute walk test (6MWT) bestimmte Belastbarkeit. Die bedeutendste Steigerung der LVEF nach Wiederherstellung von Sinusrhythmus war bei Patienten mit schwerer linksventrikulärer Dysfunktion zu beobachten. Das Wiederauftreten von Vorhofflimmern unterschied sich nicht zwischen Patienten mit schwerer und moderater linksventrikulärer Dysfunktion (Kaplan-Meier-Schätzung). Herzinsuffizienz-Patienten mit stabilem Sinusrhythmus nach 3 Monaten überlebten häufiger als ohne Sinusrhythmus (100% versus 74±13,0%, log rank p=0,007).

Clinical Investigations

Surgical Ablation of Atrial Fibrillation in Patients With Congestive Heart Failure

HERKO GRUBITZSCH, MD, SIMON DUSHE, MD, SVEN BEHOLZ, MD, PhD, PASCAL M. DOHMEN, MD, PhD, AND WOLFGANG KONERTZ, MD, PhD

Berlin, Germany

ABSTRACT

Background: Congestive heart failure (CHF) and atrial fibrillation (AF), both of which cause morbidity and mortality, are mutually promoting diseases. We aimed to evaluate surgical AF ablation in CHF.

Methods and Results: Among 212 patients (age 69 ± 8.8 years, 87% with persistent AF) undergoing concomitant left atrial (LA) ablation, 79 (37.3%) presented CHF (n = 62 with a left ventricular ejection fraction [LVEF] 0.31−0.45, n = 17 with an LVEF ≤ 0.30). Patients with CHF were similar to controls regarding AF duration (61 ± 65.1 months vs. 54 ± 67.2 months, not significant [NS]), LA diameter (49 ± 7.5 mm vs. 50 ± 9.2 mm, NS), and heart rate (78 ± 18.4 min^{-1} vs. 81 ± 21.3 min^{-1}, NS), but they required more circulatory support (17.7% vs. 1.5%, $P < .001$) and a longer intensive care unit stay (6 ± 9.5 days vs. 4 ± 10.5 days, $P = .032$). At follow-up after 13 ± 7.3 months, 42 patients (66%) with CHF and 81 controls (74%, NS) were in sinus rhythm (SR) (55% and 64% without antiarrhythmic drugs, respectively, NS). Univariate and logistic regression analysis revealed that AF duration and LA diameter predicted rhythm outcome but not CHF. In patients with an LVEF of 0.30 or less, SR conversion significantly improved LVEF, New York Heart Association class, and Minnesota Living with Heart Failure score. Kaplan-Meier estimates suggested superior survival of patients with stable SR (100% vs. 73%, log-rank $P < .05$).

Conclusions: If patients presenting with CHF and AF require cardiac surgery, concomitant AF ablation should be considered, especially if left ventricular function is severely impaired. (*J Cardiac Fail 2007;13:509−516*)

Key Words: Cardiac surgery, concomitant ablation, rhythm control.

Despite significant advances in therapeutic interventions, congestive heart failure (CHF), the most important complication of almost all forms of heart disease, remains a leading cause of morbidity and mortality.[1,2] Atrial fibrillation (AF), per se a major health problem because of its risk of stroke and premature death, is frequently associated with CHF.[3−6] The prevalence of AF increases as the severity of CHF increases.[6] Whereas AF occurs in approximately 10% of patients with CHF in New York Heart Association (NYHA) functional class II, AF occurs in approximately 50% of patients with CHF in NYHA functional class IV.

From a pathophysiologic point of view, however, the relationship of both disease entities is characterized by a mutual advancement.[6] CHF promotes AF because the hemodynamic load and specific neuroendocrine stimulation provoke alterations in atrial electrophysiologic characteristics. AF begets CHF because the loss of atrial contraction and irregular ventricular response reduce cardiac output and tachycardia may induce cardiomyopathy. Clinical data suggest that patients with CHF accompanied by AF have a poor prognosis. Mortality (all cause, sudden death, and pump failure) and morbidity (hospitalization) in patients with CHF and AF are significantly increased.[7−9]

Because the respective incidence of CHF and AF increases with age,[5,6] and the age of patients requiring cardiac surgery is continuously increasing,[10] a growing number of patients undergoing heart surgery are affected. During the

From the Department of Cardiovascular Surgery, Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany.

Manuscript received March 11, 2007; revised manuscript received April 23, 2007; revised manuscript accepted April 24, 2007.

Reprint requests: Herko Grubitzsch, MD, Klinik für Kardiovaskuläre Chirurgie Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Charité-Platz 1, 10117 Berlin, Germany.

1071-9164/$ - see front matter

doi:10.1016/j.cardfail.2007.04.011

past decade, surgical AF treatment, initially introduced as the Maze procedure,[11] has become a less complex operation.[12–14] By using different technologies for tissue ablation and focusing the lesion pattern on the left atrium (LA), promising results have been reported.[13–16] In this study we evaluated outcome after concomitant surgical AF ablation in patients with CHF.

Methods

Patients

Between March 2002 and February 2006, a total of 212 patients (56.1% were male, age 69 ± 8.8 years) scheduled for cardiac surgery underwent concomitant AF ablation. According to established definitions,[17] the majority of patients presented with persistent AF (n = 185, 87.3%), and 27 patients had paroxysmal AF. Of all the patients, 79 (37.3%) exhibited CHF, defined as NYHA class III or higher and left ventricular ejection fraction (LVEF) of 0.45 or less, determined by ventriculography or echocardiography. Patients with CHF were further stratified according to preoperative LVEF; 62 patients had moderate left ventricular (LV) impairment (LVEF 0.31–0.45), and 17 patients had severe LV dysfunction (LVEF ≤ 0.30). Preoperative, perioperative, and follow-up data were prospectively entered into an institutional database. Informed consent regarding the operation and data acquisition was obtained from all patients. For assessment of perioperative risk, the logistic EuroSCORE was determined.[18]

Surgical Procedures and Perioperative Treatment

The detailed procedures of the study population are listed in Table 1. The authors H. G., S. D., S. B., P. D., and W. K. performed 109, 17, 42, 23, and 21 operations, respectively. For all procedures, standard normothermic cardiopulmonary bypass and warm antegrade blood cardioplegia were used. All patients underwent endocardial ablation of the LA as described in detail previously.[16] Microwave (Flex 4, Guidant Corporation, Santa Clara, Calif) or radiofrequency (Cardioblate, Medtronic Incorporation, Minneapolis, Minn) energy was applied depending on the device availability or the surgeon's discretion. The lesion pattern is depicted in Figure 1. The LA appendage was oversewn only if thrombi were inside (n = 4). The transesophageal echocardiography probe was removed during ablation to avoid esophageal injury.

Table 1. Surgical Procedures

	Overall (n = 212) % (n)	No CHF (n = 133) % (n)	CHF (n = 79) % (n)
MVP/R	39.2 (83)	42.8 (57)	32.9 (26)
Isolated	22.6 (48)	27.1 (36)	15.2 (12)
+CABG	11.3 (24)	9.8 (13)	13.9 (11)
+TVP/R (+CABG)	4.2 (9)	4.5 (6)	3.8 (3)
+Congenital	1.0 (2)	1.6 (2)	–
AVR	32.1 (68)	31.6 (42)	32.9 (26)
Isolated	18.9 (40)	20.3 (27)	16.4 (13)
+CABG	3.8 (8)	3.0 (4)	5.1 (4)
+MVP/R (+CABG, +TVP/R, +AAR)	9.4 (20)	8.2 (11)	11.4 (9)
CABG	27.8 (59)	24.1 (32)	34.2 (27)
Isolated	27.4 (58)	24.1 (32)	32.9 (26)
+Aneurysmectomy	0.5 (1)	–	1.3 (1)
Other procedures	1.0 (2)	1.6 (2)	–
Microwave ablation	51.9 (110)	52.6 (70)	50.6 (40)
Radiofrequency ablation	48.1 (102)	47.4 (63)	49.4 (39)
LA reduction plasty	1.4 (3)	1.5 (2)	1.3 (1)
Re-do surgery	7.1 (15)	6.0 (8)	8.9 (7)

CHF, congestive heart failure; MVP/R, mitral valve plasty/replacement; CABG, coronary artery bypass grafting; TVP/R, tricuspid valve plasty/replacement; AVR, aortic valve replacement; AAR, ascending aortic replacement; LA, left atrial.

All patients were anticoagulated with heparin followed by phenprocoumon with a target international normalized ratio of 2.0 to 3.0. After 3 months and stable sinus or atrial-driven pacemaker rhythm in Holter electrocardiogram and mechanical atrial function in echocardiogram, anticoagulation was ceased. Patients with mechanical valve substitutes were prescribed phenprocoumon permanently (international normalized ratio of 2.5–3.5 for aortic valve prostheses and 3.0–4.0 for mitral valve prostheses). Direct current shock cardioversion of early recurrent AF was performed if the patient was symptomatic or hemodynamically compromised. Perioperatively, either preoperative beta-blocker treatment was continued or antiarrhythmic treatment with class III antiarrhythmic drugs (sotalol or amiodarone) was initiated. The decision was left to the discretion of the surgeon. After discharge, the patient's general physician or cardiologist managed the anticoagulation and antiarrhythmic therapy.

Follow-Up

Prospective follow-up was performed at 3, 6, and 12 months and annually thereafter. Patients were interviewed and underwent clinical examination, electrocardiography, and transthoracic echocardiography. In 9 patients (4.2%) who were unable to visit the clinic, interviewing was done by telephone and echocardiographic data were obtained from the referring cardiologist. Ablation was considered successful if sinus rhythm (SR) was maintained with

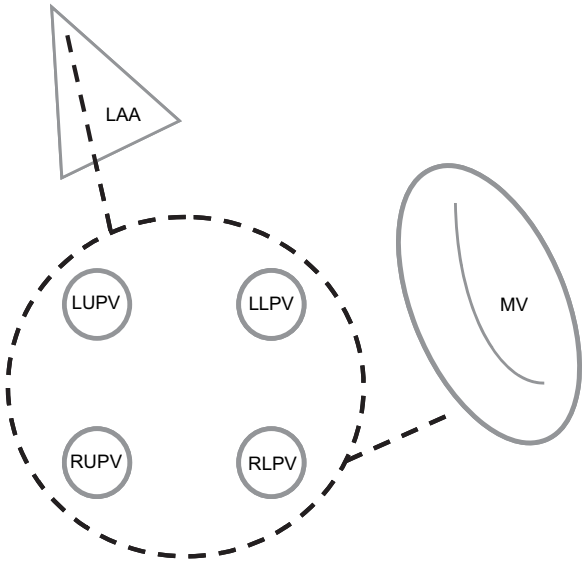

Fig. 1. Lesion pattern of LA endocardial ablation. The lesion pattern consisted of (I) LA posterior wall ablation isolating all pulmonary vein ostia, (II) a line into the LA appendage, and (III) a line to the mitral valve annulus (P3). LAA, left atrial appendage; MV, mitral valve; LUPV, left upper pulmonary vein; LLPV, left lower pulmonary vein; RUPV, right upper pulmonary vein; RLPV, right lower pulmonary vein.

no symptomatic or documented episodes of AF or atrial flutter. Any regular atrial-driven rhythm, including atrial (n = 1), atrioventricular (n = 3), or atrial triggered ventricular (n = 4) pacing, was regarded as SR.

The Minnesota Living with Heart Failure (MLHF) questionnaire was applied to assess the effects of heart failure on patients' quality of life.[19] In addition to the overall score, a physical dimension score (items 2−7, 12, and 13) and an emotional dimension score (items 17−21) were determined. The 6-minute walk test (6MWT) was used to measure patients' functional capacity.[20]

Echocardiography

Preoperatively, before discharge, and at follow-up, all patients underwent transthoracic echocardiography with the HP Sonos 5500 (Hewlett Packard, Andover, Mass). LA and LV diameter were measured using standard techniques. LVEF was assessed by the Simpson method. For assessment of LA function, the pulsed-wave signal of diastolic transmitral flow was used. Maximal flow velocities of E and A waves were measured, and E/A ratio was calculated.

Statistical Analysis

Unless otherwise indicated, data are presented as mean ± standard deviation or absolute and relative frequencies. For comparison between groups, the Mann-Whitney *U* test (continuous variables) and chi-square test (categoric variables) were used. For comparison of follow-up and preoperative data within groups, the Wilcoxon rank-sum test was applied. All tests of significance were 2 tailed, and a *P* value less than .05 was considered significant. Binary logistic regression analysis was used for identifying factors predicting SR conversion. Factors found significant ($P < .05$) on univariate analyses were entered in the multivariate analyses to identify independent risk factors. The odds ratios (ORs), 95% confidence intervals (CIs), and *P* values were calculated for each risk factor. During follow-up, cumulative mortality and freedom from recurrent AF were calculated according to the Kaplan-Meier method. Differences were analyzed by log-rank test. Statistical analysis was performed with the Statistical Package for the Social Sciences 13.0 for Windows (SPSS Inc., Chicago, Ill).

Results

Patient Groups

Baseline characteristics are presented in Table 2. AF duration and LA size, 2 important AF criteria, were similar in patients with CHF and patients without CHF. In the CHF group, the percentage of men and patients with coronary artery disease and previous myocardial infarction was higher. Obviously, patients with CHF demonstrated clinical and echocardiographic signs of a significantly advanced LV dysfunction and higher perioperative risk according to EuroSCORE. Almost all patients with persistent AF presented adequate rate control at baseline with a heart rate of 78 ± 18.4 min^{-1} (range 42−140 min^{-1}) and 81 ± 21.3 min^{-1} (range 42−126 min^{-1}) in the CHF and control groups, respectively ($P = .761$). Medical treatment in the CHF and control groups consisted of beta-blockers in 57 and 98 patients (72.1% and 73.7%, $P = .807$), digitalis in 36 and 63 patients (45.6% and 47.4%, $P = .799$), class III antiarrhythmic drugs in 5 and 6 patients (6.3% and 4.5%, $P = .818$), and other antiarrhythmic drugs in 3 and 12 patients (3.8% and 9.0%, $P = .151$), respectively. All patients with CHF and 104 control patients (78.2%) were treated with angiotensin-converting enzyme inhibitors or AT_1 receptor blockers preoperatively ($P < .001$).

Table 2. Baseline Data

		No CHF (n = 133)	CHF (n = 79)	*P*
Age	y	69 ± 9.6	70 ± 7.4	.238
Male gender	% (n)	47.4 (63)	70.9 (56)	.009
Body surface area	m^2	1.9 ± 0.23	1.9 ± 0.19	.210
Coronary artery disease	% (n)	39.8 (53)	60.8 (48)	.003
MVD	% (n)	71.7 (38)	81.2 (39)	.252
Previous MI	% (n)	66.0 (35)	85.4 (41)	.024
Mitral valve disease	% (n)	51.1 (68)	44.3 (35)	.336
Aortic valve disease	% (n)	30.8 (41)	32.9 (26)	.752
Others	% (n)	7.5 (10)	7.6 (6)	.195
Previous embolism	% (n)	2.2 (3)	1.3 (1)	.145
Persistent AF	% (n)	85.0 (113)	91.1 (72)	.192
AF duration	mo	54 ± 67.2	61 ± 65.1	.256
LA diameter	mm	50 ± 9.2	49 ± 7.5	.663
LVEF		0.58 ± 0.068	0.37 ± 0.082	<.001
LVEDD	mm	51 ± 9.3	58 ± 7.6	<.001
NYHA class		2.8 ± 0.81	3.2 ± 0.67	.002
Logistic EuroSCORE	%	7.3 ± 6.70	12.0 ± 11.91	<.001

CHF, congestive heart failure; MVD, multiple vessel disease; MI, myocardial infarction; AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association.

Overall Procedural Outcome

In patients with CHF and without CHF, there was no difference in aortic crossclamp time (84 ± 29.2 minutes and 84 ± 32.4 minutes, $P = .557$), cardiopulmonary bypass time (116 ± 32.0 minutes and 114 ± 37.2 minutes, $P = .689$), and operation time (216 ± 58.2 minutes and 212 ± 56.3 minutes, $P = .584$). Postablation treatment with antiarrhythmic drugs or beta-blockers was similar in both groups (Table 3). In 6 patients with normal LV function, a dual-chamber pacemaker was implanted for sinus node dysfunction. In 1 patient with CHF, a single-chamber pacemaker was implanted for treatment of bradyarrhythmia.

Although there was a general trend to increased perioperative morbidity in the CHF group, only the incidence of heart failure requiring inotropic and mechanical circulatory support reached statistical significance. Overall, 5 patients presented cerebral ischemic events: 2 strokes (on postoperative days 1 and 5) and 3 transient neurologic deficits (on postoperative days 2, 3, and 6). Multiple thromboembolism caused by hereditary thrombotic thrombocytopenic purpura occurred in 1 of these patients on postoperative day 5. In patients with CHF, the intensive care unit stay was increased and there was a nonsignificant trend to prolonged hospitalization. Furthermore, perioperative mortality was approximately twice as high as in patients without CHF (statistically not significant) and predominantly the result of LV dysfunction.

Table 3. Perioperative Data

		No CHF (n = 133)	CHF (n = 79)	*P*
Beta-blocker	% (n)	26.2 (33)	32.4 (23)	.354
Class III antiarrhythmic drugs	% (n)	57.1 (72)	63.4 (45)	.786
Sotalol	% (n)	73.6 (53)	73.3 (33)	.911
Amiodarone	% (n)	26.4 (19)	26.7 (12)	.506
DC shock cardioversion	% (n)	3.8 (5)	5.1 (4)	.232
Pacemaker implantation	% (n)	4.5 (6)	1.3 (1)	.198
Reexploration for bleeding	% (n)	1.5 (2)	2.5 (2)	.204
Pericardial effusion	% (n)	1.5 (2)	–	–
Heart failure	% (n)	1.5 (2)	17.7 (14)	<.001
Inotropic support	% (n)	1.5 (2)	17.7 (14)	<.001
IABP	% (n)	0.8 (1)	5.1 (4)	.045
LVAD	% (n)	–	2.5 (2)	–
Pulmonary failure	% (n)	–	5.1 (4)	–
Renal failure	% (n)	6.0 (8)	12.6 (10)	.093
Cerebrovascular accident	% (n)	2.2 (3)	2.5 (2)	.768
Intracerebral hemorrhage	% (n)	0.8 (1)	–	–
Infection	% (n)	3.0 (4)	5.1 (4)	.332
Mediastinitis	% (n)	0.8 (1)	1.3 (1)	.686
Bronchopulmonary infection	% (n)	2.2 (3)	3.8 (3)	.239
Sepsis	% (n)	1.5 (2)	3.8 (3)	.478
Mechanical ventilation time	h	14 ± 6.4	14 ± 9.8	.744
ICU stay	d	4 ± 10.5	6 ± 9.5	.032
Hospital stay	d	12 ± 13.3	19 ± 44.5	.830
Mortality (30 d)	% (n)	5.3 (7)	10.1 (8)	.182
Cardiac death	% (n)	–	6.4 (5)	–
Heart failure	% (n)	–	5.1 (4)	–
Arrhythmia	% (n)	–	1.3 (1)	–
Noncardiac death	% (n)	5.3 (7)	8.8 (3)	.626

IABP, intraaortic balloon pump; LVAD, left ventricular assist device; DC, direct current; ICU, intensive care unit.

Follow-up was 96% complete; 3 patients with CHF and 6 control patients were lost. During follow-up, 7 patients (9.8%) with CHF died of heart failure (n = 4), pneumonia (n = 2), and sepsis after major abdominal surgery (n = 1). Causes of late death in patients with normal LV function (n = 7, 5.6%, $P = .259$) were heart failure (n = 1), pneumonia (n = 2), multiple organ failure after major abdominal surgery (n = 1), cerebral hemorrhage (n = 1), and unknown (n = 2). Thromboembolic complications did not occur in either group.

At the latest available follow-up (13 ± 7.3 months), 42 patients (66%) with CHF and 81 controls (74%, $P = .301$) were in SR, 55% and 64% without antiarrhythmic drugs, respectively ($P = .234$). The results regarding rhythm outcome are shown in Table 4. More than 90% of patients in SR presented normal atrial contraction. According to LVEF, impaired ventricular function significantly recovered from 0.37 ± 0.08 to 0.47 ± 0.11 in the CHF group ($P < .001$). Although NYHA class remained inferior in the CHF group compared with the control group, it was not significantly different. Compared with baseline, a reduction of LA size was observed in all patients by approximately 16% ($P < .001$), whereas neither group showed changes in LV size.

Univariate analysis of potential determinants for SR conversion demonstrated no association between clinical or echocardiographic parameters of CHF and rhythm outcome (Table 5). The weak trend to higher SR conversion rate in patients with coronary artery disease could not be confirmed by logistic regression analysis. Only AF duration (OR 1.014, 95% CI 1.007−1.020, $P < .001$) and LA diameter (OR 1.063, 95% CI 1.013−1.116, $P = .013$) were independent factors for AF persistence.

Table 4. Follow-Up Data

		No CHF (n = 110)	CHF (n = 64)	*P*
Sinus rhythm	% (n)	73.6 (81)	65.6 (42)	.301
Atrial contraction	% (n)	90.7 (68)	94.6 (35)	.876
E/A ratio		2.4 ± 0.85	2.2 ± 0.70	.200
Atrial fibrillation	% (n)	22.7 (25)	28.1 (18)	.289
Atrial flutter	% (n)	3.6 (4)	1.6 (1)	.197
NYHA class		1.9 ± 0.65*	1.7 ± 0.66*	.166
LA diameter	mm	42 ± 6.7*	42 ± 7.7*	.952
LVEF		0.55 ± 0.106†	0.47 ± 0.112*	<.001
LVEDD	mm	50 ± 8.6†	56 ± 10.0†	<.001

CHF, congestive heart failure; E/A ratio, ratio of maximal flow velocities of early (E) and atrial (A) diastolic transmitral flow signal assessed by pulsed-wave Doppler; NYHA, New York Heart Association; LA, left atrium; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

Assessment of LA function by pulsed-wave Doppler failed in 5 and 6 patients in the CHF and non-CHF groups, respectively.

*$P < .001$, comparison with preoperative data by Wilcoxon rank-sum test.

†P = NS, comparison with preoperative data by Wilcoxon rank-sum test.

Restoration of Sinus Rhythm in Congestive Heart Failure

Although regaining SR was associated with a significant lower NYHA class and MLHF score in patients with severe CHF, it had no influence in patients with moderate CHF (Fig. 2). Similarly, SR led to an improved MLHF score on the physical component in patients with severe CHF (9 ± 11.7 vs. 26 ± 9.2, $P = .062$) but not in patients with moderate CHF (11 ± 11.9 vs. 10 ± 12.1, $P = .827$). SR had no influence on the emotional component of the MLHF score in either group. According to the results of the 6MWT, exercise capacity remained unchanged by SR

Table 5. Univariate Analysis of Preoperative Variables for Rhythm Outcome

		SR (n = 123)	Non-SR (n = 51)	*P*
Age	y	68 ± 9.4	70 ± 6.8	.231
Male gender	% (n)	52.8 (65)	64.7 (33)	.151
Coronary artery disease	% (n)	53.6 (66)	39.2 (20)	.083
Mitral valve disease	% (n)	48.0 (59)	45.1 (23)	.729
Aortic valve disease	% (n)	28.4 (35)	25.5 (13)	.690
Persistent AF	% (n)	97.6 (120)	96.1 (49)	.594
AF duration	mo	41 ± 51.1	104 ± 104.4	<.001
LA diameter	mm	48 ± 8.1	52 ± 9.0	.031
LVEF		0.51 ± 0.122	0.49 ± 0.128	.266
LVEDD	mm	54 ± 9.1	56 ± 9.3	.188
NYHA class		3.0 ± 0.74	2.8 ± 0.77	.396
Logistic EuroSCORE	%	7.7 ± 8.28	8.2 ± 6.68	.657

SR, sinus rhythm; AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association.

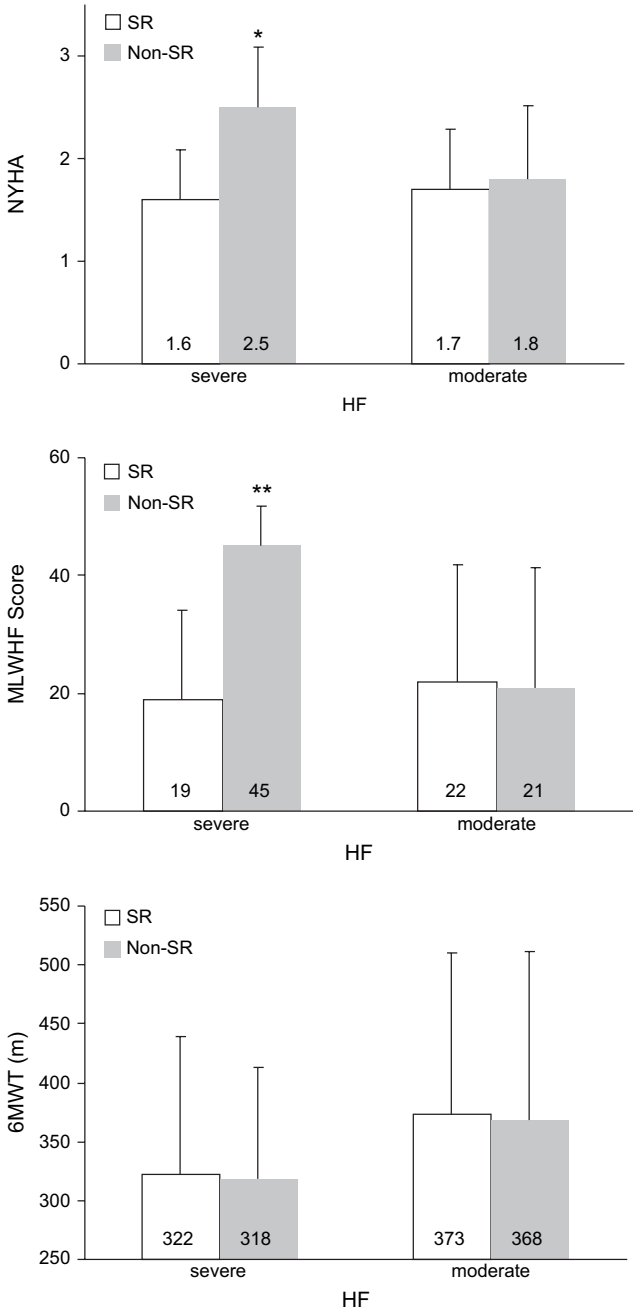

Fig. 2. Clinical outcome after SR restoration in CHF. *P = .005. **P = .016. SR, sinus rhythm; CHF, congestive heart failure; NYHA, New York Heart Association; MLHF, Minnesota Living with Heart Failure; 6MWT, 6-minute walk test.

conversion in patients with severe and moderate CHF (Fig. 2).

Changes of LV function and dimensions in patients with severe and moderate CHF in relation to SR restoration are depicted in Figure 3. The most significant increase of LVEF, which occurred within the first 3 months and remained stable thereafter, was observed in patients with severe CHF (Fig. 3A, top). However, SR conversion had no influence on LVEF in patients with moderate CHF or on LV size in either group.

Kaplan-Meier estimates of the time to recurrence of persistent AF among patients with CHF demonstrated no difference in subgroups with moderately or severely depressed LV function (Fig. 4A). Patients in whom stable SR was present 3 months after ablation demonstrated significantly improved survival compared with patients without SR (100% vs. 74% ± 13.0%, P = .007, Fig. 4B). This result did not depend on age or degree of CHF, because patients with SR did not differ from patients without SR regarding age (71 ± 7.5 years vs. 71 ± 5.3 years, P = .927) and LVEF at baseline (0.36 ± 0.09 vs. 0.37 ± 0.08, P = .809) or in NYHA functional class (1.7 ± 0.64 vs. 1.8 ± 0.75, P = .648), MLHF score (27 ± 22.4 vs. 28 ± 20.3, P = .843), 6MWT (330 ± 131.0 m vs. 392 ± 117.1 m, P = .343), and LVEF (0.47 ± 0.11 vs. 0.52 ± 0.10, P = .162) at follow-up.

Discussion

Although the AFFIRM study (a large-scale randomized trial of 4060 patients) showed that treatment with a rhythm-control strategy offered no survival advantage over a rate-control strategy in an intention-to-treat analysis of patients with AF and a high risk for stroke or death, an ‘‘on-treatment’’ analysis revealed that SR was associated with a lower risk of death.[21,22] In addition to the general risk for morbidity and mortality due to thromboembolism, there are several sequelae of AF that are liable to aggravate LV dysfunction and lead to a worse prognosis.[6] Loss of atrial contraction and atrioventricular synchrony, as well as irregular ventricular response, reduce stroke volume and elevate filling pressure. Tachyarrhythmia may lead to tachycardia-induced cardiomyopathy. Vice versa, CHF can beget AF as hemodynamic load and changes in neurohormonal activation predispose one to alterations in atrial electrophysiologic parameters, in particular refractory period, conduction time, heterogeneity of depolarization and repolarization, and automaticity. Thus, restoration of SR seems to be a reasonable approach in patients presenting with AF.

This study of patients with CHF and AF undergoing cardiac surgery and concomitant AF ablation revealed the following key findings: (1) Restoration of SR was successful in 66% of patients with CHF (55% without antiarrhythmic drugs) and led to atrial contraction in the majority of patients (95%). (2) Patients with heart failure in whom SR was successfully restored and maintained demonstrated beneficial midterm survival. (3) SR restoration was accompanied by significant improvements of NYHA functional class, MLHF score, and LVEF in patients with advanced LV dysfunction. On the other hand, the procedure was associated with an increased perioperative risk in patients with CHF compared with control patients.

There have been few reports on the restoration of SR without antiarrhythmic drugs in patients with AF and CHF.[23,24] Hsu and colleagues[23] reported that SR was successfully restored by catheter ablation in 78% of patients

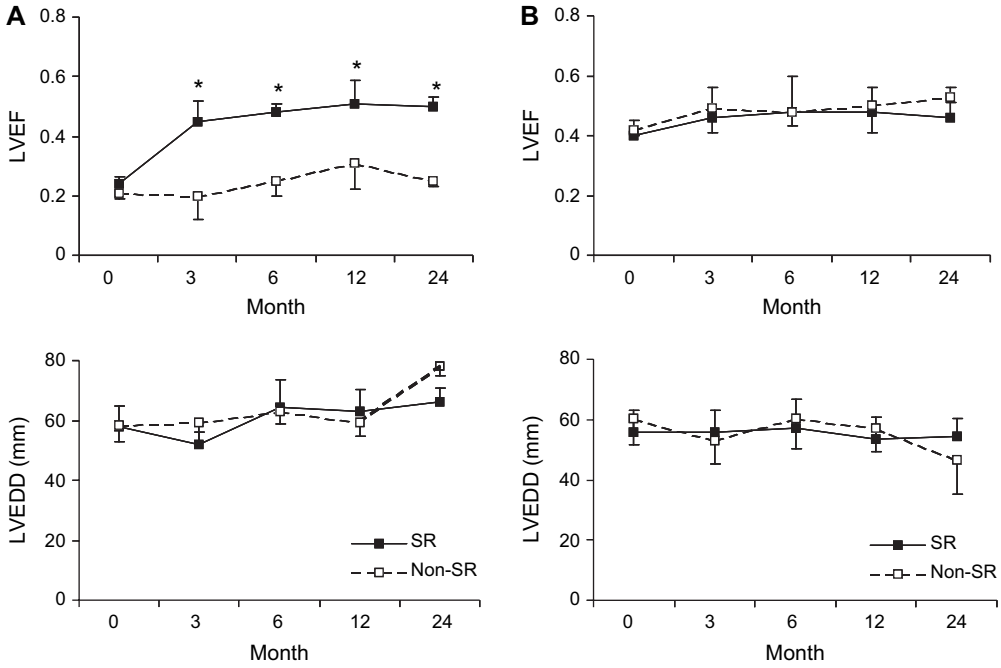

Fig. 3. LV function and dimension after SR restoration in CHF. A: Results in patients with severe CHF (LVEF ≤ 0.30). B: Results in patients with moderate CHF (LVEF 0.31−0.45). *$P < .05$. SR, sinus rhythm; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; CHF, congestive heart failure.

with CHF. In view of the success rate in our cohort, one has to consider that patients treated by catheter ablation were remarkably younger (56 ± 10 years) and presented less frequently with structural heart disease. Similarly, Hsu and colleagues found a somewhat superior SR conversion rate in control patients (84%), but this difference was not statistically significant. As our data show, CHF per se is not a determinant of procedural success. In fact, mainly preoperative AF duration and LA size are predictors for rhythm outcome after surgical AF ablation, as demonstrated previously.[16,25] The interpretation of our results must not ignore primary cardiac surgery. This might account for the restoration and maintenance of SR, as for any detected improvement in ventricular function (see below), but we are unable to assess its relative contribution as opposed to the ablation procedure itself. However, although more patients with CHF presented coronary artery disease and previous myocardial infarction (Table 2), the distribution of surgical procedures was comparable in the CHF and control groups (Table 1). After the Cox-Maze procedure to treat AF in a small series of patients with CHF, normal SR was restored in 76% of patients after 63 months of follow-up.[24] Again, these patients were younger (median age 55 years) and underwent mostly isolated arrhythmia surgery; only 7 patients required concomitant coronary artery bypass grafting. The biatrial lesion set of the Cox operation in contrast with our strict LA approach could be a further explanation for the difference in SR conversion rate. However, it has been demonstrated that AF will not recur if macro-reentry can be prevented by lesions critically placed in the LA.[13]

By using antiarrhythmic drugs, randomized trials showed improved survival among patients with CHF and AF who had a reversion to SR.[26,27] In the recently reported substudy of the AFFIRM trial, the benefit of reduced risk of death with SR restoration was reversed by the continued use of antiarrhythmic drugs and presence of heart failure.[22] With catheter ablation or the Cox-Maze operation as nonpharmacologic AF treatment, survival benefits have not been demonstrated so far.[23,24] For the first time, our data suggest improved survival with SR restoration after surgical AF ablation. Other variables, such as age or parameters of LV dysfunction, had no influence. However, because this study is limited by the sample size and nonrandomized design, this result has to be interpreted with caution. When survival is assessed, the perioperative risk has to be considered as well. According to the EuroSCORE, mainly LV dysfunction, age, and nonisolated coronary artery surgery predicted an early mortality of 26.1% ± 18.71% in our patients with CHF and 14.5% ± 10.94% in our patients without CHF who died perioperatively ($P = .206$). Furthermore, as reported recently, AF per se seems to be a marker for higher operative risk.[28,29] On the contrary, the impact of AF ablation on perioperative mortality remains rather unclear.

In the present study, restoration of SR resulted in renormalization of atrial function in almost all patients and an overall increase in LVEF of 27% in patients with CHF, even in the presence of adequate ventricular rate control in the majority of patients before operation. This result may highlight the contribution of atrial contraction and atrioventricular synchrony to cardiac output and, vice versa,

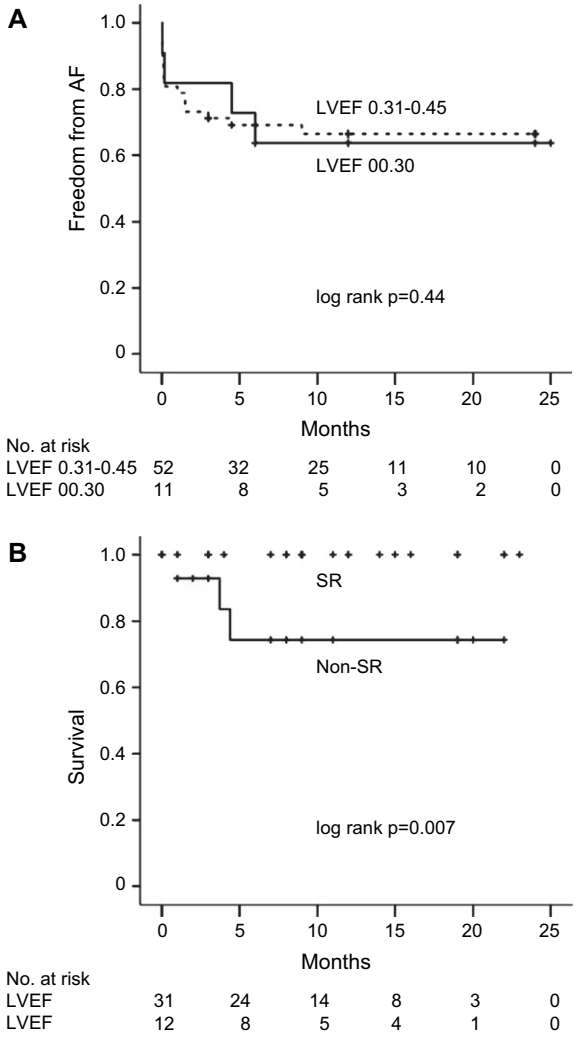

Fig. 4. Kaplan-Meier estimates. A: Time to recurrence of persistent AF in patients with moderate and severe CHF. B: Survival of patients with CHF according to rhythm outcome (SR/non-SR) at 3 months after AF ablation. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; SR, sinus rhythm.

the pathophysiologic role of AF in LV dysfunction. Accordingly, we observed the most striking improvement in LVEF (by ∼88%), accompanied by significant symptomatic improvement according to NYHA class and MLHF score, in patients with severely impaired LV function if SR was restored. This is identical to the finding of Stulak and colleagues,[24] who reported significant improvement in LVEF after the Cox-Maze procedure in patients with AF who had the most severe LV impairment preoperatively (LVEF $\leq$ 0.35). In our study, NYHA class and MLHF score reached the same level in patients with severe CHF and successful SR conversion as in patients with moderate CHF; only functional capacity according to the 6MWT remained somewhat inferior. In patients with moderate CHF, restoration of SR was not associated with additional reversal of LV dysfunction or further clinical improvement, suggesting that loss of atrial function can be tolerated if LV function is not severely impaired. Nevertheless, even these patients exhibited an improved clinical outcome after surgical treatment of structural heart disease.

Because this study is a retrospective analysis of prospectively collected data, it has general limitations inherent to observational studies in nonrandomized patient groups. Thus, it is unclear how the results can be generalized to all patients with CHF and AF requiring cardiac surgery. Moreover, we are unable to draw conclusions on whether rhythm control or rate control should be the preferred strategy for AF treatment in patients with CHF. This question is addressed in the ongoing Atrial Fibrillation and Congestive Heart Failure trial, and its results will facilitate decision making in these cases.[30]

Although there are no controlled trial data comparing newer ablative sources and the cut-and-sew technique, it is obvious that ablation of atrial tissue by various technologies is far less invasive than the complex Cox-Maze procedure. In particular, the risk of operating on thin atrial tissue is removed. Ablation allows concomitant AF treatment in almost all patients undergoing cardiac surgery. However, preoperative identification of patients with heart failure in whom concomitant AF ablation will improve outcome is indeed challenging, especially if perioperative risk and a certain percentage of patients remaining in AF are considered. Nevertheless, our finding that patients with severe LV dysfunction and AF predominantly benefit from SR restoration in addition to surgery for structural heart disease, even if the heart rate is controlled before operation, suggests the integration of concomitant AF ablation is a reasonable treatment strategy in patients with CHF and AF who are referred for cardiac surgery.

Acknowledgments

The authors thank Ms. Doreen Boettner for excellent coordination of patient follow-up.

References

1. Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J 1991;121:951−7.
2. Spencer FA, Meyer TE, Goldberg AJ, et al. Twenty year trends (1975-1995) in the incidence, in-hospital, and long-term death rates associated with heart failure complicating acute myocardial infarction. J Am Coll Cardiol 1999;34:1378−87.
3. Chesebro JH, Fuster V, Halperin JL. Atrial fibrillation—risk marker for stroke. N Engl J Med 1990;323:1556−8.
4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946−52.
5. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82:2N−9N.
6. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(suppl):2D−8D.
7. Middlekauf HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. Circulation 1991;84:40−8.

8. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol 1998;32: 695−703.
9. Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older persons with atrial fibrillation versus sinus rhythm. Am J Cardiol 2001;87:224−5.
10. Kalmar P, Irrgang E. Cardiac surgery in Germany during 2003: a report by the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2004;52:312−7.
11. Cox JL, Schuessler RB, D'Agostino HJ Jr, et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569−83.
12. Spitzer SG, Richter P, Knaut M, Schüler S. Treatment of atrial fibrillation in open heart surgery. The potential role of microwave energy. Thorac Cardiovasc Surg 1999;47(Suppl 3):374−8.
13. Kottkamp H, Hindricks G, Hammel D, et al. Intraoperative radiofrequency ablation of chronic atrial fibrillation: a left atrial curative approach by elimination of anatomic anchor reentrant circuits. J Cardiovasc Electrophysiol 1999;10:772−80.
14. Khargi K, Deneke T, Haardt H, et al. Saline-irrigated, cooled-tip radiofrequency ablation is an effective technique to perform the maze procedure; a prospective randomised study. Ann Thorac Surg 2001;72: S1090−5.
15. Mohr FW, Fabricius AM, Falk V, et al. Curative treatment of atrial fibrillation with intraoperative radiofrequency ablation. J Thorac Cardiovasc Surg 2002;123:919−27.
16. Grubitzsch H, Beholz S, Dohmen PM, Dushe S, Liu J, Konertz W. Ablation of atrial fibrillation in valvular heart surgery: are results determined by underlying valve disease? J Heart Valve Dis 2007;16:76−83.
17. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol 2006;48:e149−246.
18. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9−13.
19. Rector TS. A conceptional model of the quality of life in relation to heart failure. J Card Fail 2005;11:173−6.
20. Enright PL. The six-minute walk test. Respir Care 2003;48:783−5.
21. Wyse DG, Waldo AL, DiMarco JP, et al, for the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825−33.
22. Corley SD, Epstein AE, DiMarco JP, et al, for the AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Circulation 2004;109:1509−13.
23. Hsu LF, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004;351:2373−83.
24. Stulak JM, Dearani JA, Daly RC, Zehr KJ, Sundt TM, Schaff HV. Left ventricular dysfunction in atrial fibrillation: restoration of sinus rhythm by the Cox-Maze procedure significantly improves systolic function and functional status. Ann Thorac Surg 2006;82: 494−501.
25. Chen MC, Chang JP, Chang HW, et al. Clinical determinants of sinus conversion by radiofrequency maze procedure for persistent atrial fibrillation in patients undergoing concomitant mitral valvular surgery. Am J Cardiol 2005;96:1553−7.
26. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observation from the Veterans Affairs Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT). Circulation 1998;98: 2574−9.
27. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patient with reduced left ventricular function: a Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) substudy. Circulation 2001;104:292−6.
28. Quader MA, McCarthy PM, Gillinov AM, et al. Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? Ann Thorac Surg 2004;77:1514−24.
29. Levy F, Garayalde E, Quere JP, Ianetta-Peltier M, Peltier M, Tribouilloy C. Prognostic value of preoperative atrial fibrillation in patients with aortic stenosis and low ejection fraction having aortic valve replacement. Am J Cardiol 2006;98:809−11.
30. The AF-CHF Trial Investigators. Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial. Am Heart J 2002;144:597−607.

3. Diskussion

Die chirurgische Behandlung des Vorhofflimmerns hat sich in der letzten Dekade durch Entwicklung verschiedener Ablationstechnologien vor allem als begleitende Therapie bei herzchirurgischen Eingriffen weit verbreitet (30-36). So wurden 2009 in den herzchirurgischen Kliniken Deutschlands bereits 4153 Ablationen durchgeführt (8). Das Prinzip der verschiedenen Verfahren besteht in der Schaffung linienförmiger atrialer Läsionen mit daraus resultierender Fibrosierung. Diese Narben dienen der elektrischen Isolierung ektoper Herde arrhythmogener Aktivität sowie der Unterbrechung chronifizierter kreisender Erregungen. Trotz hoher Erfolgsraten kann eine Wiederherstellung des Sinusrhythmus nicht bei allen Patienten erreicht werden. Das Vorhofflimmern kann fortbestehen oder im Verlauf wieder auftreten (29, 33, 34, 37). Nach pathophysiologischen und klinischen Faktoren dafür wurde in den vorliegenden Arbeiten gesucht. Welche Bedeutung die begleitende chirurgische Ablationsbehandlung bei in ihrer Prognose deutlich eingeschränkten Patienten mit Vorhofflimmern und Herzinsuffizienz hat, wurde als weiterer Schwerpunkt evaluiert.

Verglichen mit Sinusrhythmus ist Vorhofflimmern mit deutlichen Veränderungen auf elektrophysiologischer, kontraktiler und struktureller Ebene assoziiert (18, 20, 39-41). Dieses atriale Remodeling, das sowohl durch die Arrhythmie selbst als auch durch zugrundeliegende Herzerkrankungen induziert wird, bestimmt die typische Progression des Vorhofflimmerns (18).

Während des Übergangs von Sinusrhythmus zu intermittierendem und weiter zu persistierendem Vorhofflimmern wurden eine Verkürzung der atrialen effektiven Refraktärzeit, eine Abnahme der Leitungsgeschwindigkeit und ein Anstieg der atrialen Fibrillationsfrequenz als Charakteristika des elektrischen Remodeling beschrieben (39, 40). Diese Veränderungen, die auf einer verkürzten Aktionspotentialdauer durch reduzierten Ca^{2+}-Einstrom und erhöhten K^{+}-Ausstrom sowie einer verlangsamten Reizweiterleitung durch verminderten Na^{+}-Einstrom und Dysfunktion der gap junctions (Connexine) basieren (42), stellen fundamentale Determinanten für Reentry dar. Das erklärt, warum Erkrankungen, die ähnliche Veränderungen auf zellulärem Niveau hervorrufen - z.B. Verminderung des Na^{+}-Einstroms durch Herzinsuffizienz - zu Vorhofflimmern prädisponieren (42).

Die atriale Refraktärzeit und die Leitungsgeschwindigkeit können am Patienten nicht oder nur mit sehr aufwendigen Methoden bestimmt werden. Demgegenüber erwies sich

unter Anwendung hoch-verstärkter und hoch-auflösender EKG-Geräte mit nachfolgender Extraktion des Vorhofsignals und spektraler Frequenzanalyse (Fourier-Transformation) die Bestimmung der atrialen Fibrillationsfrequenz als praktikables Verfahren zur individuellen Evaluation des elektrischen Remodeling (19). Nachdem wir die klinische Anwendbarkeit des CardioLink®-EKG-Systems zeigen konnten, fanden wir eine signifikant schmalere Konfiguration der Peak-Frequenzkomponente bei höherer fibrillatorischer Aktivität. Scheinbar nimmt die Heterogenität der atrialen Aktivität mit steigender Fibrillationsfrequenz ab. Ähnlich fanden Sasaki et al. (43) eine parallele Abnahme der AFZL und ihres Variationskoeffizienten. Das heißt, Aktivitäten mit einer kurzen Zykluslänge dominieren und führen möglicherweise zur Unterdrückung von Aktivitäten mit langer AFZL.

Mit der natürlichen Progression des Vorhofflimmerns treten zeitabhängig Veränderungen von elektrophysiologischen Parametern auf. So ist kürzer bestehendes persistierendes Vorhofflimmern mit einer geringeren Fibrillationsfrequenz verbunden als länger bestehendes und die mittlere AFZL nimmt mit der Zeit ab (21, 43). Wir beobachteten einerseits einen nicht-signifikanten Trend zu einer höheren Fibrillationsfrequenz mit längerer Vorhofflimmerdauer (2.1.1.). Andererseits war bei unseren Mitralklappenpatienten (2.1.2.) und anderen Kohorten (39) keine Beziehung zwischen Vorhofflimmerdauer und Fibrillationsfrequenz nachweisbar. Als mögliche Ursache muss man in Betracht ziehen, dass die AFZL bei länger bestehendem Vorhofflimmern (>3 Monate) oft nahe der physiologischen Frequenzgrenze liegt, was die Erfassung von Unterschieden erschwert. So scheinen nach unseren Daten auch weitere klinische Charakteristika wie Herzfrequenz, Alter, Geschlecht, Vorhofgröße, Funktion des linken Ventrikels, Art der zugrundeliegenden Herzerkrankung oder die Medikation (Betablocker) bei länger bestehendem Vorhofflimmern keinen Einfluss mehr auf die Fibrillationsfrequenz auszuüben.

Mit der Bestimmung der atrialen fibrillatorischen Aktivität aus dem Oberflächen-EKG ist es möglich, die Wirkung von Antiarrhythmika zu überwachen und Patienten zu identifizieren, die für eine pharmakologische Kardioversion geeignet sind (19, 38, 39, 44, 45). Aus diesen Untersuchungen kann geschlossen werden, dass die „Konversionsschwelle“ nach medikamentös induzierter Frequenzsenkung bei einer AFZL zwischen 250 und 300 ms liegt. Die mittlere Zykluslänge unserer Patienten (2.1.2.), die Sinusrhythmus wiedererlangten (155±23,2 ms) oder nicht (150±16,0 ms) war von dieser Schwelle weit entfernt und überschritt nicht 247 ms. Dies kann erklären,

warum es nicht möglich war, einen Einfluss der atrialen fibrillatorischen Aktivität auf die Sinusrhythmus-Konversion nachzuweisen. Umgekehrt wurde gezeigt, dass eine hohe Fibrillationsfrequenz (≥420 fpm; einer AFZL von ≤143 ms entsprechend) ein Risikofaktor für Wiederauftreten von Vorhofflimmern nach elektrischer Kardioversion ist (45).

Verglichen mit Sinusrhythmus ist die atriale Kontraktilität von Patienten mit persistierendem Vorhofflimmern deutlich reduziert, was durch einen verminderten Ca^{2+}-Einstrom bedingt wird, der wahrscheinlich aus quantitativen und/oder funktionellen Veränderungen der L-Typ-Ca^{2+}-Kanäle resultiert (20, 42). So wird einerseits die unter Umständen letale Ca^{2+}-Überladung der Zelle verhindert. Andererseits begünstigt die Hypokontraktilität eine Dilatation der Vorhöfe, die sowohl Raum für Reentry-Pfade bietet und somit Vorhofflimmern unterhalten kann als auch einen Promotor für strukturelle Gewebsveränderungen darstellt (20, 42, 46).

Echokardiografische Untersuchungen nach Kardioversion zeigten, dass sich die atriale kontraktile Dysfunktion innerhalb von 24 Stunden komplett erholt, wenn Vorhofflimmern bis zu zwei Wochen bestand, während die Erholung über einen Monat dauert, wenn Vorhofflimmern mehr als 6 Wochen persistierte (47). Eine Beziehung zwischen kontraktilen Eigenschaften und Dauer des Vorhofflimmerns konnten wir nicht nachweisen (2.1.2.). Weiterhin war die atriale Kontraktilität nicht mit anderen Parametern des Remodeling bzw. der hämodynamischen Belastung assoziiert. Der Nachweis signifikanter Unterschiede kann – ähnlich wie bei der AFZL - fehlgeschlagen sein, weil die kontraktile Dysfunktion fortgeschritten und nahe ihres Tiefpunktes war. Der Trend in der univariaten Analyse zu höherer atrialer Kontraktilität bei Patienten, die Sinusrhythmus wiedererlangten, suggeriert, dass Vorhofflimmern in einem früheren Stadium des kontraktilen Remodeling leichter terminiert werden kann.

Die Dilatation der Vorhöfe ist das makroskopisch auffallende Zeichen des strukturellen Umbaus (41, 48, 49). Histologisch imponiert neben myolytischen Myozyten mit signifikantem Verlust kontraktiler Elemente und Glykogeneinlagerungen vor allem eine interstitielle Fibrose (41). Solche strukturellen Veränderungen können auch durch andere Erkrankungen oder Alter verursacht werden, die damit die Suszeptibilität für Vorhofflimmern erhöhen (18, 50). Mitralklappenerkrankungen führen über eine Erhöhung des linksatrialen Druckes zur Dilatation des Vorhofs und zur atrialen Fibrose, was die Assoziation zwischen Mitralvitien und dieser Rhythmusstörung erklärt (5, 50). Ähnlich erklärt sich der Zusammenhang zwischen Herzinsuffizienz und Vorhofflimmern. Die durch Aktivierung des lokalen Renin-Angiotensin-Aldosteron-Systems

hervorgerufene interstitielle Fibrose ist durch Störung der regionalen atrialen Leitungseigenschaften ein wesentliches Substrat für Reentry (18, 51).

Strukturelle Veränderungen der Myozyten und des Interstitiums entwickeln sich gewöhnlich über Monate, während Anpassungen auf elektrophysiologischem und kontraktilem Niveau sofort nach Beginn des Vorhofflimmerns auftreten (18, 41). Ähnlich renormalisieren sich die elektrophysiologischen Parameter nach der Wiederherstellung von Sinusrhythmus rasch und vollständig, während die Rückbildung der strukturellen Veränderungen Zeit beansprucht und oft nur inkomplett erfolgt (52). Das erklärt, weshalb strukturelle Veränderungen einen entscheidenden Faktor für die Entwicklung von permanentem Vorhofflimmern darstellen (18, 41). Unsere Ergebnisse und Berichte anderer Autoren (22, 53-55) zeigen, dass sie auch ein wesentlicher Prädiktor sowohl für die Terminierung als auch für das Wiederauftreten von Vorhofflimmern sind.

Obwohl an gut definierten Tiermodellen von Kurzzeit-Vorhofflimmern eine enge Beziehung zwischen den verschiedenen Remodeling-Ebenen nachgewiesen wurde (56), gelang dies in klinischen Studien nicht (21). Wie in unseren Patienten scheinen die hohe interindividuelle Variabilität sowohl der Remodeling-Parameter als auch der Dauer des Vorhofflimmerns sowie zusätzliche patienten- und erkrankungsbezogene Faktoren den Nachweis einer vermuteten Beziehung zu erschweren. Die Ergebnisse der Vorhofablation als Begleitprozedur herzchirurgischer Eingriffe werden jedoch vom Ausmaß des atrialen Remodeling auf struktureller Ebene und der präoperativen Dauer der Arrhythmie bestimmt, so dass diese Parameter orientierend zur individuellen Therapieplanung herangezogen werden können. Dagegen erscheint bei fehlender Ergebnisrelevanz die individuelle Bestimmung des elektrischen und kontraktilen Remodeling nicht sinnvoll.

In früheren Arbeiten wurden die höchsten Sinusrhythmus-Konversionsraten nach Vorhofablation im Zusammenhang mit Mitralklappeneingriffen beobachtet (33, 34). Zieht man die linksatriale hämodynamische Belastung, die aus Mitralvitien resultiert, in Betracht, erscheint ein solcher Zusammenhang zunächst offensichtlich. Andererseits wurde auch berichtet, dass die Vorhofablation in Kombination mit einem Aortenklappenersatz bzw. einer koronaren Bypass-Operation ebenso effektiv war wie bei Mitralklappeneingriffen (57, 58). Unsere Analyse von Patienten mit Klappeneingriffen und Vorhofablation (2.2.1.) schloss sowohl eine bestimmte Valvulopathie als auch andere Variablen, wie Alter, linksventrikuläre Ejektionsfraktion und EuroSCORE, als Faktor für eine erfolgreiche Sinusrhythmus-Konversion aus. Dagegen erwiesen sich die

präoperative Vorhofflimmerdauer und die Größe des linken Vorhofs als unabhängige Prädiktoren für die Persistenz von Vorhofflimmern. So zeigten 86% der Patienten, bei denen Vorhofflimmern nicht länger als zwei Jahre bestanden hatte, zur Nachuntersuchung Sinusrhythmus. Ähnlich wurde von anderen gezeigt, dass die Dauer des Vorhofflimmerns einer der bedeutendsten Prädiktoren für ein Vorhofflimmer-Rezidiv nach Cox-Maze-Operation im Allgemeinen und in Kombination mit Mitralklappeneingriffen ist (53, 54). Für Mitralklappeneingriffe und begleitende Radiofrequenz-Maze-Prozeduren wurde die Bedeutung der Vorhofflimmer-Dauer und der Größe des linken Vorhofs für die Sinusrhythmus-Konversion von Chen et al. gezeigt: eine kürzere Vorhofflimmerdauer (<66 Monate) und eine kleinere Vorhofgröße (<56,8 mm anteroposteriorer Diameter) waren mit überlegenen Ergebnissen hinsichtlich Vorhofflimmer-Freiheit nach fünf Jahren von 87,5% bzw. 88,5% verbunden (55).

Für die Zeit bis zum Wiederauftreten von Vorhofflimmern nach begleitender Vorhofablation waren von zahlreichen potentiellen Faktoren, die untersucht wurden, nur die präoperative Dauer des Vorhofflimmerns und die Größe des linken Vorhofs signifikante Determinanten (2.2.2.). Jede Erhöhung der Vorhofflimmer-Dauer um einen Monat korrespondierte mit einer Erhöhung des Risikos für rekurrentes Vorhofflimmern von 0,5% und jede Vergrößerung des linken Vorhofs um einen Millimeter mit einer 5,6%igen Risikoerhöhung. Bisher wurden die präoperative Dauer des Vorhofflimmerns und die Größe des linken Vorhofs nur für biatriale Maze-Prozeduren, die entweder mit cut-and-sew- oder Ablationstechnik ausgeführt wurden, als entscheidende Prädiktoren für rekurrentes Vorhofflimmern nachgewiesen (53-55, 59). Für linksatriale Ablationen wurden bislang das Patientenalter, rheumatische Mitralklappenerkrankungen, frühere Mitralklappeneingriffe, das Läsionsmuster, die LVEF und Vorhofflimmern zum Zeitpunkt der Entlassung als prädiktive Faktoren beschrieben (60, 61). Als Ursache dafür muss man in Betracht ziehen, dass nur bei 67% bzw. 73% der Patienten dieser Studien permanentes Vorhofflimmern bestand, was den Einfluss der Vorhofflimmerdauer oder der Vorhofgröße überwogen haben mag. Manasse et al. benutzten verschiedene Läsionsmuster, die das Ergebnis mit höherer Wahrscheinlichkeit bestimmt haben als die Vorhofflimmerkriterien (60). Für die Anwendung alternativer Ablationstechnologien wurde die Bedeutung der linksatrialen Läsionen mit weiter Isolation der Pulmonalvenen, mindestens einer Verbindungslinie zwischen rechten und linken Pulmonalvenen und einer Verbindungslinie zum Mitralklappenring gezeigt (62). Die alleinige Pulmonalvenenisolation und Läsionsmuster, die keine Läsion zum Mitralklappenring

beinhalteten sind weniger effektiv zur Behandlung von permanentem Vorhofflimmern (62).

Zusätzlich zum Thromboembolie-assoziierten Morbiditäts- und Letalitätsrisiko ergeben sich aus Vorhofflimmern Folgen, die eine linksventrikuläre Dysfunktion verstärken und deren Prognose verschlechtern können (9). Der Verlust der atrialen Kontraktion, die fehlende atrioventrikuläre Synchronisation und die irreguläre Ventrikelaktion reduzieren das Schlagvolumen und erhöhen den Füllungsdruck. Eine Tachyarrhythmie kann zu tachykardie-induzierter Kardiomyopathie führen. Umgekehrt prädisponieren bei Herzinsuffizienz nicht nur der typische strukturelle Umbau (interstitielle Fibrose), sondern auch elektrophysiologische Veränderungen wie eine verlängerte atriale Leitungszeit oder eine Sinusknotendysfunktion zu Vorhofflimmern (63).

Bisher liegen nur wenige Berichte zur Katheterablation bzw. chirurgischen Therapie als nicht-pharmakologische Methoden zur Behandlung von Patienten mit Vorhofflimmern und Herzinsuffizienz vor (64-67). Hsu et al. berichteten, dass Sinusrhythmus in 78% der Herzinsuffizienz-Patienten wiederhergestellt werden konnte (64). Mit Blick auf die Erfolgsrate in unserer Kohorte muss man in Betracht ziehen, dass die mit Katheterablation behandelten Patienten deutlich jünger waren (56±10 Jahre) und seltener eine strukturelle Herzerkrankung aufwiesen. Auch Hsu et al. fanden eine etwas höhere Sinusrhythmuskonversionsrate bei Kontroll-Patienten (84%), aber dieser Unterschied war statistisch nicht signifikant. Wie unsere Daten zeigen, ist die Herzinsuffizienz per se kein Prädiktor für den Erfolg der Prozedur. Nach Cox-Maze-Operation zur Behandlung von Vorhofflimmern in einer kleinen Serie von Herzinsuffizienz-Patienten konnte nach 63 Monaten Nachbeobachtung in 76% Sinusrhythmus wiederhergestellt werden (65). Wiederum handelte es sich um jüngere Patienten (Median des Alters 55 Jahre). Diese unterzogen sich zudem vorwiegend einem isolierten rhythmuschirurgischen Eingriff; nur bei 7 Patienten war begleitend eine Koronarrevaskularisation erforderlich.

Die Interpretation unserer Ergebnisse – sowohl bezüglich Wiederherstellung und Erhalt des Sinusrhythmus als auch hinsichtlich einer verbesserten linksventrikulären Funktion - darf nicht die Bedeutung des eigentlichen herzchirurgischen Eingriffs unterschätzen. Allerdings ist es unmöglich, den relativen Beitrag der Hauptprozedur gegenüber der Ablation anzugeben. Dennoch, obwohl mehr Herzinsuffizienz-Patienten eine koronare Herzerkrankung und frühere Myokardinfarkte aufwiesen, war die Verteilung der chirurgischen Eingriffe in der Herzinsuffizienz- bzw. Kontroll-Gruppe vergleichbar.

Bezogen auf die Letalität zeigten Antiarrhythmika zur Wiederherstellung bzw. zum Erhalt von Sinusrhythmus (Rhythmuskontrolle) bisher keinen Vorteil gegenüber der reinen pharmakologischen Frequenzkontrolle. Insbesondere konnte die AF-CHF-Studie, eine multizentrische, prospektive, randomisierte Studie von 1376 Patienten mit Herzinsuffizienz und einer LVEF von ≤35% sowie einer kürzlichen Vorhofflimmer-Episode keine Überlegenheit einer Rhythmuskontrolle mittels Amiodaron, Sotalol oder Dofetilide nachweisen (68). Allerdings muss man u.a. kritisieren, dass die Rhythmusanalyse lediglich mittels 12-Kanal-EKG erfolgte (Übersehen von Vorhofflimmer-Episoden) und die Rhythmuszuordnung in beiden Gruppen nicht eindeutig war (ca. 20% Vorhofflimmern in der Rhythmus-Kontroll-Gruppe versus ca. 60% in der Frequenz-Kontroll-Gruppe). Auch wenn Amiodaron als sicherstes und effektivstes Antiarrhythmikum für Patienten mit Vorhofflimmern und Herzinsuffizienz gilt, müssen das ungünstige Nebenwirkungsprofil und die Effekte auf das Überleben kritisch bewertet werden. Bezüglich der Letalität unter Amiodaron existieren sowohl Hinweise für eine Reduktion als auch für eine Erhöhung (69, 70). Grundsätzlich ist der prognostisch ungünstige Effekt von Antiaarrhythmika für Patienten mit Herzinsuffizienz seit längerem bekannt (71). In der „on-treatment“-Analyse der AFFIRM-Studie wurde der Nutzen eines durch Wiederherstellung von Sinusrhythmus reduzierten Sterberisikos durch fortgesetzte Einnahme von Antiarrhythmika aufgehoben (72).

Die nicht-pharmakologische Behandlung von Vorhofflimmern mittels interventioneller Ablation bzw. chirurgischer Therapie wurde bisher nicht in randomisierten Studien hinsichtlich Überlebensvorteile untersucht (64-67). Unsere Daten weisen auf eine Prognoseverbesserung durch Wiederherstellung des Sinusrhythmus nach chirurgischer Vorhofablation hin. Andere Variablen, wie Alter oder Parameter der linksventrikulären Dysfunktion, zeigten keinen Einfluss. Dieses Ergebnis muss vorsichtig interpretiert werden, da die Studie durch Patientenzahl und fehlende Randomisierung limitiert ist. Zur Einschätzung des Überlebens muss auch die perioperative Letalität berücksichtigt werden. Gemäß EuroSCORE wurde die Letalität der perioperativ verstorbenen Patienten hauptsächlich vom Ausmaß der linksventrikulären Dysfunktion, dem Alter und kombinierten Koronareingriffen bestimmt. Außerdem scheint Vorhofflimmern per se einen Marker für ein höheres Operationsrisiko darzustellen (6, 73).

In unserer Studie führte die Wiederherstellung von Sinusrhythmus zur Renormalisierung der atrialen Funktion bei fast allen Patienten und zu einer Gesamtzunahme der LVEF in Höhe von 27% bei herzinsuffizienten Patienten, trotz präoperativ adäquater Kontrolle

der Herzfrequenz bei der Mehrheit der Patienten. Dieses Ergebnis veranschaulicht den Beitrag der atrialen Kontraktion und der atrioventrikulären Synchronität zum kardialen Auswurf und – umgekehrt – die pathophysiologische Rolle des Vorhofflimmerns bei linksventrikulärer Dysfunktion. Dementsprechend wurde die deutlichste LVEF-Steigerung (um ca. 88%), die mit signifikanter symptomatischer Verbesserung (NYHA-Klasse und MLHF Score) einherging, bei Patienten mit schwer eingeschränkter LV-Funktion beobachtet, wenn Sinusrhythmus wiederhergestellt war. Das ist übereinstimmend mit den Ergebnissen von Stulak et al. (65).

Deshalb sollte trotz des erhöhten perioperativen Risikos die begleitende Vorhofablation bei Patienten mit Herzinsuffizienz und Vorhofflimmern, die sich einem herzchirurgischen Eingriff unterziehen müssen, in Betracht gezogen werden.

4. Zusammenfassung

Die Therapie von Vorhofflimmern erlangt einerseits aufgrund der zunehmenden Prävalenz dieser Arrhythmie mit steigendem Lebensalter und der häufigen Assoziation mit strukturellen Herzerkrankungen sowie neuer Behandlungsverfahren andererseits wachsende Bedeutung. Im letzten Jahrzehnt hat die chirurgische Therapie von Vorhofflimmern durch die Entwicklung verschiedener Ablationsverfahren stark zugenommen und gute Ergebnisse erreicht. Bei einem Teil der Patienten kann jedoch Sinusrhythmus nicht wiederhergestellt werden bzw. Vorhofflimmern tritt im Verlauf erneut auf. Für Patienten mit chronischer Herzinsuffizienz und Vorhofflimmern ist die Bedeutung der begleitend zum herzchirurgischen Eingriff erfolgten Vorhofablation offen.

Die vorliegenden, durchweg an Patienten mit Vorhofflimmern und strukturellen Herzerkrankungen durchgeführten Untersuchungen zeigen, dass, dem pathophysiologischen Konzept des atrialen Remodeling folgend, Veränderungen auf elektrischer, kontraktiler und struktureller Ebene nachweisbar sind, die durch eine hohe interindividuelle Variabilität charakterisiert sind. Dabei ließen sich keine Beziehungen zwischen verschiedenen Remodeling-Ebenen sowie Beziehungen zwischen Remodeling und Dauer des Vorhofflimmerns bzw. linksatrialer hämodynamischer Last aufzeigen. Strukturelle, nicht aber elektrische bzw. kontraktile atriale Veränderungen weisen neben der präoperativen Dauer der Arrhythmie einen prädiktiven Charakter für die Wiederherstellung von Sinusrhythmus nach chirurgischer Ablation zur Therapie permanenten Vorhofflimmerns auf.

Die Untersuchung klinischer Faktoren schloss Alter, Geschlecht, die primäre Herzerkrankung, stattgehabte thromboembolische Ereignisse oder Kardioversionen, Begleiterkrankungen, EuroSCORE, die linksventrikuläre Größe und Funktion, die Aortenklemmzeit, die Ablationstechnologie und die Behandlung mit Antiarrhythmika als Prädiktor für das Rhythmusergebnis aus. Dagegen erwiesen sich die präoperative Dauer des Vorhofflimmerns und der linksatriale Durchmesser als relevante Faktoren sowohl für die Sinusrhythmus-Konversion als auch für die Zeit bis zum Wiederauftreten von Vorhofflimmern.

Vor allem Patienten mit schwerer linksventrikulärer Dysfunktion und Vorhofflimmern profitieren von einer Wiederherstellung des Sinusrhythmus, auch wenn die Herzfrequenz präoperativ kontrolliert war. Neben einer deutlichen Verbesserung der NYHA-Klasse und des MLHF-Gesamtpunktwertes ist eine Erholung der

linksventrikulären Funktion zu verzeichnen. Der Hinweis, dass stabiler Sinusrhythmus im Verlauf bei Herzinsuffizienz-Patienten prognostisch überlegen ist, muss an größeren Kohorten und möglichst unter kontrollierten Bedingungen untersucht werden.

Relevanz der Studien

Das Ausmaß des atrialen Remodeling auf struktureller Ebene und die präoperative Dauer der Arrhythmie können orientierend zur individuellen Therapieplanung herangezogen werden, da diese Parameter die Ergebnisse der chirurgischen Ablation zur Behandlung von permanentem Vorhofflimmern als Begleitprozedur herzchirurgischer Eingriffe wesentlich beeinflussen. Dagegen erscheint bei fehlender Ergebnisrelevanz die individuelle Bestimmung des elektrischen und kontraktilen Remodeling nicht sinnvoll. Aufgrund ihrer Resultate erlangt die begleitende Vorhofablation einen Platz in der herzchirurgischen Behandlung von Patienten mit Herzinsuffizienz und Vorhofflimmern.

5. Literaturangaben

1 Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol 2006; 48: 854-906. [Erratum, J Am Coll Cardiol 2007; 50: 562.]

2 Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N-9N.

3 Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006; 27: 949-953.

4 Levy S. Factors predisposing to the development of atrial fibrillation. Pacing Clin Electrophysiol 1997; 20: 2670-2674.

5 Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL, Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002; 40: 84-92.

6 Quader MA, McCarthy PM, Gillinov AM, Alster JM, Cosgrove DM 3rd, Lytle BW, Blackstone EH: Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? Ann Thorac Surg 2004, 77:1514-1524.

7 Ngaage DL, Schaff HV, Barnes SA, Sundt III TM, Mullany CJ, Dearani JA, Daly RC, Orszulak TA. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery? Ann Thorac Surg 2006; 82: 1392-1399.

8 Gummert JF, Funkat A, Beckmann A, Schiller W, Hekmat K, Ernst M, Beyersdorf F. Cardiac surgery in Germany during 2009: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiov Surg 2010; 58: 379-386.

9 Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91 (suppl): 2D-8D.

10 Prystowsky EN, Katz A. Atrial Fibrillation. In: Topol EJ (ed.). Textbook of Cardiovascular Medicine. 2nd ed. Lippincott Williams & Wilkins 2002: pp1050-1068.

11 Wolf PA, Abbot RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983-988.

12 Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tacy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors for congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol. 2000; 35: 1628-1637.

13 Benjamin EJ, Wolf PA, D´Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998; 98: 946–952.

14 Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo AL. Pathophysiology and Prevention of Atrial Fibrillation. Circulation 2001; 103: 769-777.

15 Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002; 415: 219-226.

16 Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998; 339: 659-666.

17 Schmitt C, Ndrepepa G, Weber S, Schmieder S, Weyerbrock S, Schneider M, Karch MR, Deisenhofer I, Schreieck J, Zrenner B, Schömig A. Biatrial multisite mapping of atrial premature complexes triggering onset of atrial fibrillation. Am J Cardiol 2002; 89: 1381-1387.

18 Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodelling during atrial fibrillation. Cardiovasc Res 2002; 54: 230-246.

19 Bollmann A, Husser D, Stridh M, Soernmo L, Majic M, Klein HU, Olsson SB. Frequency measures obtained from the surface electrocardiogramm in atrial fibrillation research and clinical decision making. J Cardiovasc Electrophysiol 2003; 14 (Suppl.): S154-S161.

20 Schotten U, Ausma J, Stellbrink C, Sabatschus I, Vogel M, Frechen D, Schoendube F, Hanrath P, Allessie MA. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. Circulation 2001; 103: 691-698.

21 Bollmann A, Kanuru NK, McTeague KK, Walter PF, DeLurgio DB, Langberg JJ. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. Am J Cardiol 1998; 81: 1439-1445.

22 Bollmann A, Binias KH, Toepffer I, Molling J, Geller C, Klein HU. Importance of left atrial diameter and atrial fibrillatory frequency for conversion of persistent atrial fibrillation with oral flecainide. Am J Cardiol 2002; 90: 1011-1014.

23 Middlekauf HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. Circulation 1991; 84: 40-48.

24 Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol 1998; 32: 695-703.

25 Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older persons with atrial fibrillation versus sinus rhythm. Am J Cardiol 2001; 87: 224-225.

26 Cox JL. Surgical treatment of atrial fibrillation: a review. Europace 2004; 5: 20-29.

27 Cox JL, Schuessler RB, D'Agostino HJ jr, Stone CM, Chang BC, Cain ME, Corr PB, Boineau JP. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991; 101: 569-583.

28 Cox JL, Schuessler RB, Lappas DG, Boineau JP. An 8 ½-year clinical experience with surgery for atrial fibrillation. Ann Surg 1996; 224: 267-273.

29 Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. Eur J Cardiothorac Surg. 2005; 27: 258-265.

30 Knaut M, Spitzer SG, Karolyi L, Ebert HH, Richter P Tugtekin SM, Schüler S. Intraoperative microwave ablation for curative treatment of atrial fibrillation in open heart surgery - the MICRO-STAF and MICRO-PASS pilot trial. MICROwave Application in Surgical treatment of Atrial Fibrillation. MICROwave Application for

the Treatment of Atrial Fibrillation in Bypass-Surgery. Thorac Cardiovasc Surg. 1999; 47 Suppl 3: 379-384.

31 Pasic M, Bergs P, Müller P, Hofmann M, Grauhan O, Kuppe H, Hetzer R. Intraoperative radiofrequency maze ablation for atrial fibrillation: the Berlin modification. Ann Thorac Surg. 2001; 72: 1484-1490; discussion 1490-1.

32 Khargi K, Deneke T, Haardt H, Lemke B, Grewe P, Müller KM, Laczkovics A. Saline-irrigated, cooled-tip radiofrequency ablation is an effective technique to perform the maze procedure. Ann Thorac Surg. 2001; 72: S1090-1095.

33 Mohr FW, Fabricius AM, Falk V, Autschbach R, Doll N, von Oppell U, Diegeler A, Kottkamp H, Hindricks G. Curative treatment of atrial fibrillation with intraoperative radiofrequency ablation: short-term and mid-term results. J Thorac Cardiovasc Surg 2002; 123: 919-927.

34 Sie HT, Beukema WP, Elvan A, Misier ARR. Long-term results of irrigated radiofrequency modified maze procedure in 200 patients with concomitant cardiac surgery: six years experience. Ann Thorac Surg 2004; 77: 512-517.

35 Ninet J, Roques X, Seitelberger R, Deville C, Pomar JL, Robin J, Jegaden O, Wellens F, Wolner E, Vedrinne C, Gottardi R, Orrit J, Billes MA, Hoffmann DA, Cox JL, Champsaur GL. Surgical ablation of atrial fibrillation with off-pump, epicardial, high-intensity focused ultrasound: results of a multicenter trial. J Thorac Cardiovasc Surg. 2005; 130: 803-809.

36 Doll N, Kiaii BB, Fabricius AM, Bucerius J, Kornherr P, Krakor R, Gummert JF, Walther T, Mohr FW. Intraoperative left atrial ablation (for atrial fibrillation) using a new argon cryocatheter: early clinical experience. Ann Thorac Surg. 2003; 76: 1711-1715; discussion 1715.

37 Knaut M, Tugtekin SM, Jung F, Matschke K. Microwave ablation for the surgical treatment of permanent atrial fibrillation--a single centre experience. Eur J Cardiothorac Surg. 2004; 26: 742-746.

38 Holm M, Pehrson S, Ingemansson M, Sörnmo L, Johansson R, Sandhall L, Sunemark M, Smideberg B, Olsson C, Olsson SB. Non-invasive assessment of the atrial cycle length during atrial fibrillation in man: introducing, validating and illustrating a new ECG method. Cardiovasc Res 1998; 38: 69-81.

39 Bollmann A, Sonne K, Esperer HD, Toepffer I, Langberg JJ, Klein HU. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG. Cardiovasc Res 1999; 44: 60-66.

40 Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92: 1954-1968.

41 Corradi D, Callegari S, Maestri R, Benussi S, Alfieri O. Structural remodelling in atrial fibrillation. Nature Clinical Practice Cardiovascular medicine 2008; 5: 782-796.

42 Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodelling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev 2007; 87: 425-456.

43 Sasaki T, Niwano S, Sasaki S, Imaki R, Yuge M, Hirasawa S, Satoh D, Moriguchi M, Fujiki A, Izumi T. Long-term follow-up of changes in fibrillation waves in patients with persistent atrial fibrillation – spectral analysis of surface ECG. Circ J 2006; 70: 169-173.

44 Fujiki A, Nagasawa H, Sakabe M, Sakurai K, Nishida K, Mizumaki K, Inoue H. Spectral characteristics of human atrial fibrillation waves of the right atrial free wall with respect to the duration of atrial fibrillation and effect of class I antiarrhythmic drugs. Jpn Circ J 2001; 65: 1047-1051.

45 Bollmann A, Mende M, Neugebauer A, Pfeiffer D. Atrial fibrillatory frequency predicts atrial defibrillation threshold and early arrhythmia recurrence in patients

undergoing internal cardioversion of persistent atrial fibrillation. Pacing Clin Electrophysiol 2002; 25: 1179-1184.

46 Sun H, Gaspo R, Leblanc N, Nattel S. Cellular mechanisms of atrial contractile dysfunction caused by sustained atrial tachycardia. Circulation 1998; 98: 719-727.

47 Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, Munson JT, Douglas PS. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994; 23: 1535-1540.

48 Davies MJ, Pomerance A: Pathology of atrial fibrillation in man. Br Heart J 1972; 34: 520-525.

49 Schotten U, de Haan S, Neuberger HR, Eijsbouts S, Blaauw Y, Tieleman R, Allessie M. Loss of atrial contractility is primary cause of atrial dilatation during first days of atrial fibrillation. Am J Physiol Heart Circ Physiol 2004; 287: H2324-H2331.

50 Bailey GWH, Braniff BA, Hancock EW, Cohn KE. Relation of left atrial pathology to atrial fibrillation in mitral valvular disease. Ann Intern Med 1968; 69: 13-20.

51 Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynaminc nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation 2002; 105: 2672-2678.

52 Ausma J, van der Velden HM, Lenders MH, van Ankeren EP, Jongsma HJ, Ramaekers FC, Borgers M, Allessie MA. Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the goat. Circulation 2003; 107: 2051-2058.

53 Gaynor SL, Schuessler RB, Bailey MS, Ishii Y, Boineau JP, Gleva MJ, Cox JL, Damiano RJ Jr. Surgical treatment of atrial fibrillation: predictors of late recurrence. J Thorac Cardiovasc Surg 2005; 129: 104-111.

54 Gillinov AM, Sirak J, Blackstone EH, McCarthy PM, Rajeswaran J, Pettersson G, Sabik FJ 3rd, Svensson LG, Navia JL, Cosgrove DM, Marrouche N, Natale A. The Cox maze procedure in mitral valve disease: predictors of recurrent atrial fibrillation. J Thorac Cardiovasc Surg 2005; 130: 1635-1660.

55 Chen MC, Chang JP, Chang HW, Chen CJ, Yang CH, Chen YH, Fu M. Clinical determinants of sinus conversion by radiofrequency maze procedure for persistent atrial fibrillation in patients undergoing concomitant mitral valvular surgery. Am J Cardiol 2005; 96: 1553-1557.

56 Schotten U, Duytschaever M, Ausma J, Eijsbouts S, Neuberger HR, Allessie M. Electrical and contractile remodelling during the first days of atrial fibrillation go hand-in-hand. Circulation 2003; 107: 1433-1439.

57 Geidel S, Ostermeyer J, Lass M, Geisler M, Kotetishvili N, Aslan H, Boczor S, Kuck KH. Permanent atrial fibrillation ablation surgery in CABG and aortic valve patients is at least as effective as in mitral valve disease. Thorac Cardiovasc Surg 2006; 54: 91-95.

58 Khargi K, Lemke B, Deneke T. Concomitant antiarrhythmic procedures to treat permanent atrial fibrillation in CABG and AVR patients are as effective as in mitral valve patients. Eur J Cardiothorac Surg 2005; 27: 841-846.

59 Kamata J Kawazoe K, Izumoto H, Kitahara H, Shiina Y, Sato Y, Nakai K, Ohkubo T, Tsuji I, Hiramori K. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operartions. Ann Thorac Surg 1997; 64: 394-398.

60 Manasse E, Gaita F, Ghiselli S, Barbone A, Garberoglio L, Citterio E, Ornaghi D, Gallotti R. Cryoablation of the left posterior atrial wall: 95 patients and 3 years of mean follow-up. Eur J Cardiothorac Surg 2003; 24: 731-740.

61 Fayad G, Le Tourneau T, Modine T, Azzaoui R, Ennezat PV, Decoene C, Deklunder G, Warembourg H. Endocardial radiofrequency ablation during mitral

valve surgery: effect on cardiac rhythm, atrial size, and function. Ann Thorac Surg 2005; 79: 1505-1511.

62 Gillinov AM, Bhavani S, Blackstone E, Rajeswaran J, Svensson LG, Navia JL, Pettersson BG, Sabik JF, Smedira NG, Mihaljevic T, McCarthy PM, Shewchick J, Natale A. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. Ann Thorac Surg 2006; 82: 502-514.

63 Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrical remodelling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation 2003; 108: 1461-1468.

64 Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié JL, Scavée C, Bordachar P, Clémenty J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004; 351: 2437-40.

65 Stulak JM, Dearani JA, Daly RC, Zehr KJ, Sundt TM, Schaff HV. Left ventricular dysfunction in atrial fibrillation: restoration of sinus rhythm by the Cox-Maze procedure significantly improves systolic function and functional status. Ann Thorac Surg 2006; 82: 494-501.

66 Chen MS, Marrouche NF, Kaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004; 17: 1004-1009.

67 Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18: 9-14.

68 Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O´Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL, for the Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008; 358: 2667-2677.

69 Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Lancet 1997; 350: 1417-1724.

70 Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225-237.

71 Stevenson WG, Stevenson LW, Middlekauf HR, Fonarow GC, Hamilton MA, Woo MA, Saxon LA, Natterson PD, Steimle A, Walden JA, Tillisch JH. Improving survival for patients with atrial fibrillation and advanced heart failure. J Am Coll Cardiol 1996; 28: 1458-1463. [Erratum, J Am Coll Cardiol 1997; 30: 1902.]

72 Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG for the AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Circulation 2004; 109: 1509-1513.

73 Levy F, Garayalde E, Quere JP, Ianetta-Peltier M, Peltier M, Tribouilloy C. Prognostic value of preoperative atrial fibrillation in patients with aortic stenosis

and low ejection fraction having aortic valve replacement. Am J Cardiol 2006; 98: 809-811.

DANKSAGUNG

Ohne Unterstützung - in verschiedensten Bereichen und durch eine Reihe von Personen - wäre diese Habilitationsschrift nicht möglich gewesen. Deshalb möchte ich mich bei allen Menschen, die kurzfristig oder dauerhaft, im beruflichen Alltag oder privat zu dieser Arbeit beigetragen haben bzw. mich dazu motiviert haben, bedanken.

Herausragender Dank gilt Herrn Professor Dr. med. Wolfgang Konertz, der mir an der Charité die berufliche und wissenschaftliche Entwicklung ermöglicht und mich permanent gefördert hat. Die Implementierung und Anwendung der Verfahren zur chirurgischen Behandlung von Vorhofflimmern sowie die mit dieser Arbeit behandelten wissenschaftlichen Untersuchungen wurden von ihm engagiert unterstützt.

Des Weiteren gilt mein Dank allen Mitarbeiterinnen und Mitarbeitern der Klinik für Kardiovaskuläre Chirurgie ohne deren Zusammenarbeit die Durchführung der klinischen Untersuchungen nicht möglich gewesen wäre. Insbesondere danke ich Frau Doreen Böttner für die exzellente Organisation der Nachuntersuchungen und Terminkoordinierung sowie Herrn PD Dr. med. Diethelm Modersohn für die Anleitung und technische Hilfe im Rahmen der Messungen im Labor und im OP.

Für die angenehme Zusammenarbeit bei der Datengewinnung und den interessanten Diskussionen bedanke ich mich bei den Doktoranden Frau Jessie Michels, Herrn Konstantin Krieger und Herrn Christian Grabow sowie für die Hilfe bei der Einarbeitung in fortgeschrittene statistische Methoden bzw. deren Anwendung bei Herrn Helmut Orawa.

Viele Menschen haben mich zu meiner beruflichen und wissenschaftlichen Entwicklung motiviert. Für diese Anregungen möchte ich mich stellvertretend bei den Professoren Lothar Eckel, Hans-Georg Wollert, Christian von Heymann und Michael Sander bedanken, deren kollegiale und freundschaftliche Kooperation ich immer wieder geniessen durfte.

Aus völlig anderer Perspektive gilt mein besonderer Dank meiner Familie. Sowohl für meine Frau als auch für meine Kinder waren meine berufliche und insbesondere die wissenschaftliche Entwicklung mit zahlreichen Einschränkungen verbunden. Sie haben mich solche Auswirkungen nie spüren lassen. Im Gegenteil, sie haben mich immerfort unterstützt und mir im Alltag und bei vielen anderen Gelegenheiten Arbeit abgenommen. Diese Zuwendung hat für mich einen so hohen Wert, dass ich sie nur dankbar annehmen, aber niemals ausgleichen kann.

ERKLÄRUNG

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

22.03.2011 .....