

SCIENTIFIC LETTERS

Acute pressure overload cardiac arrhythmias are dependent on the presence of myocardial tissue catecholamines

An acute rise in aortic pressure causes ventricular arrhythmias which are suppressed by β adrenergic antagonism.^{1,2} The fact that these arrhythmias occur in isolated heart preparations,² and after stellate ganglion excision,¹ excludes the possibility that the effectiveness of β blockade could be caused by the blocking of a reflex with sympathetic efferent limb. In order to find the reason for this, we utilised the well established chronically denervated canine preparation³ in which the ventricles are almost completely depleted of catecholamines. The corresponding clinical situation is cardiac transplantation, but our study could not be performed ethically in such patients.

Beagle dogs, weighing between 13.7–17.0 kg of either sex, were denervated under 1.5% halothane in N_2O/O_2 , removing the parasympathetic preganglionic neurones and the sympathetic postganglionic neurones. Adequate postoperative pain killing drugs were administered routinely. The study was made after 3–4 weeks, when the myocardial catecholamines had depleted. Each dog (four denervated and four controls), breathing air spontaneously, was then anaesthetised with intravenous sodium methohexitone (1%) followed by intravenous chloralose (100 mg/kg). A balloon catheter was introduced from a carotid artery and positioned under fluoroscopic control in the ascending aorta. Left ventricular pressure was recorded via a Gaeltec catheter that had been introduced via a femoral artery. Mean arterial pressure was monitored from an arterial cannula via a fluid filled line connected to a Statham P23Db strain gauge transducer. A standard three lead ECG was displayed continuously and, together with the left ventricular pressure (proximal to the balloon) and mean arterial pressure (distal to the balloon), was recorded on an eight pen chart recorder (Devices M16). All animals were prepared and studied in this way, whether in the innervated or cardiac denervated state. The aortic balloon catheter was inflated using a predetermined effective volume (10–25 ml) and maintained for a standard duration of four seconds. A period of six minutes was then allowed to elapse before repeated inflations. Between the repeated inflations we checked that there were no significant changes in the left ventricular and mean arterial pressure from the initial values obtained at the beginning of the experiment. The concentrations of myocardial noradrenaline (norepinephrine) and adrenaline (epinephrine) were assessed with the use of high pressure liquid chromatography with an electrochemical detection method.

In innervated dogs, obstruction to the ascending aorta by balloon inflation increased left ventricular systolic pressure, and produced an average of 3.6 ectopic beats per balloon inflation, with varying QRS duration. In the dogs with chronically denervated hearts, similar inflation produced no, or many fewer, premature ventricular beats (average of

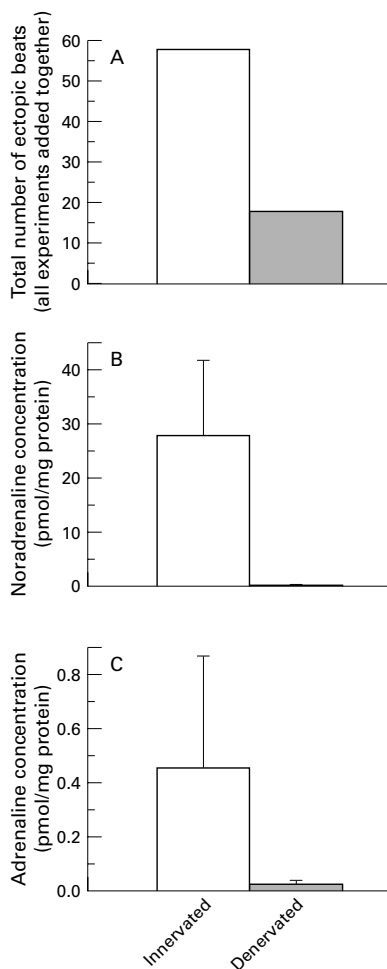


Figure 1 The reduction in the total number of ectopic beats (A) in cardiac denervated animals (grey columns) and innervated hearts (open columns) was comparable to the reduction in myocardial tissue noradrenaline (B) and adrenaline (C). All columns indicate means (1 SD). All differences were highly significant ($p < 0.005$).

0.9 per inflation). The between group F variance ratio (non-parametric analysis of variance (ANOVA)) was 76.06, which yields a probability of no difference between innervated and cardiac denervated in number of ectopic beats of 0.0001. The mean (SD) increase in systolic left ventricular pressure was not significantly different between the two groups: denervated 48.9 (19.47) mm Hg v control 51.5 (16.03) mm Hg, $p = 0.47$.

The total data for premature ventricular beats in the control and cardiac denervated dogs was compared with that for myocardial adrenaline and noradrenaline content (fig 1). In all cardiac denervated dogs these catecholamines were severely depleted, which matches previous findings in our laboratory.

This study shows that depletion of myocardial catecholamines by chronic cardiac denervation causes the left ventricle to lose most of its sensitivity to acute pressure, load induced arrhythmias. If we study the previously published records of Elzinga and colleagues⁴ we can observe analogous results in the chronically denervated heart during aortic obstruction (although this is not mentioned in that paper which was devoted to the Anrep effect). The results of the present study are compatible with the preliminary results with β blockade² in isolated hearts.

Our present results pinpoint the involvement of tissue catecholamines. We attribute the great reduction in ectopic frequency in denervated myocardium to myocardial catecholamine depletion rather than loss of sympathetic and parasympathetic afferent or efferent neuronal pathways because pressure load induced arrhythmias occur after acute denervation.^{1,2} Acute pressure loading of myocardium induces release of proarrhythmic noradrenaline from the myocardium, presumably from sympathetic neurones.⁵

A J DRAKE-HOLLAND
Cardiothoracic Surgery

MIM NOBLE
MJ LAB
Cardiovascular Medicine,
National Heart & Lung Institute,
Imperial College School of Medicine,
Charing Cross Hospital,
Fulham Palace Road,
London W6 8RF, UK
a.drake-holland@jic.ac.uk

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Non-invasive characterisation of coronary lesion morphology by multi-slice computed tomography: a promising new technology for risk stratification of patients with coronary artery disease

The non-invasive detection of coronary artery disease is a prime goal for future developments in clinical cardiology. In addition to the documentation of significant stenoses, the detection of vulnerable plaques is of major importance for risk stratification and early treatment, in order to prevent plaque ruptures.¹ Recently, a new generation of fast spiral computed tomography scanners has been introduced using a multi-slice technique (MSCT). This new technology allows for an almost motion free visualisation of the coronary arteries.^{2,3} We report on non-invasive differentiation of coronary plaque morphology by MSCT in patients with lesions in the proximal left anterior descending artery (LAD). The results were compared with the findings of intracoronary ultrasound (ICUS).

The study protocol was approved by the local ethical committee and the patients gave informed consent before inclusion in the study. All patients had chronic stable angina caused by a severe lesion in the LAD and were assigned for percutaneous transluminal coronary angioplasty (PTCA). A major inclusion criterion in the study was the presence of a clearly identifiable plaque in the proximal LAD. One plaque was selected for analysis in each patient. MSCT of the heart was performed within 24 hours before the intervention. Immediately before PTCA, ICUS was performed to analyse vessel morphology proximal to or at the target lesion. To ensure that the identical plaque

Table 1 Patient and plaque characteristics

Patient/ plaque number	Sex	Age (years)	BMI	Cardiovascular risk factors					Plaque morphology*	Plaque density (HU)†
				S	DM	H	HLP	FH		
1	Male	58	28.71	+	-	+	+	+	Soft	6 (28)
2	Female	65	27.13	-	-	+	+	-	Soft	-5 (25)
3	Male	59	23.96	-	+	-	-	-	Intermediate	83 (17)
4	Male	46	28.69	+	-	+	+	+	Intermediate	51 (19)
5	Male	63	26.76	-	-	+	+	+	Calcified	489 (372)
6	Female	70	25.78	-	+	+	+	+	Calcified	423 (111)

BMI, body mass index (kg/m²); S, smoking; DM, diabetes mellitus; H, hypertension; HLP, hyperlipoproteinaemia; FH, family history of coronary artery disease.

*Plaque morphology classified by using ICUS criteria. *Soft plaque*—more than 80% of the plaque composed of tissue with an echogenicity lower than the echogenicity of the adventitia (arc of lesion calcium < 90%). *Intermediate plaque*—more than 80% of the plaque area composed of tissue producing echoes as bright or brighter than the adventitia (arc of lesion calcium < 90%). *Calcified plaque*—plaque involving bright echoes with acoustic shadowing accompanying more than 90° of the vessel wall circumference.⁴

†Plaque density derived from density measurements performed by multi-slice computed tomography (HU, Hounsfield units).

was assessed by the different techniques, landmarks were used—that is, the origin of side branches.

Baseline angiograms of the LAD were conducted in at least two projections before the intervention. Continuous ultrasound images were received by motorised pullback of the catheter (0.5 mm/s, UltraCross 3.2 French, 30 MHz coronary imaging catheter, Scimed, Boston Scientific Corporation, San Jose, California, USA). The images were immediately digitalised by using echoPlaque Software (Indec Systems Inc, Mount View, California, USA). Plaque morphology was classified according to established ICUS criteria.⁴ Lesion severity was defined as: mild < 50%; moderate 50–75%; and severe > 75% area stenosis.

All scans of the entire heart were conducted during one breathhold (approximately 25 seconds, collimation 1.0 mm, pitch 1.5, 140 kV, 300 mAs, rotation time 500 ms, 150 ml of contrast agent) using a Somatom Volume Zoom scanner (Siemens, Forchheim, Germany). Image reconstruction was performed in the diastolic phase with a retrospective gating of 450 ms absolute reverse. For plaque detection, contrast media enhanced axial slices were analysed. To determine plaque morphology, a total of 16 density measurements within the plaque area at randomly selected points at four different axial

slices were performed. Lesion severity was defined as: mild < 50%; moderate 50–75%; and severe > 75% area stenosis.

Six plaques, detected in the proximal LAD of six patients, were analysed by comparing the results of angiography, ICUS, and MSCT. The patient characteristics are summarised in table 1.

In patients 1 and 2, angiography revealed mild atherosclerotic vessel alterations in the LAD proximal to the target lesions (fig 1). On ICUS, both plaques were classified as soft lesions. These plaques showed hypoechoic areas in the centre, suggesting the presence of lipid cores. Area stenosis was 46%/48%. These plaques were clearly detectable by MSCT, and density measurements revealed 6 (28) Hounsfield units (HU) for plaque 1 and -5 (25) HU for plaque 2. Both plaques were classified as mild lesions < 50% (table 1).

With angiography, plaque 3 was found to be a moderate lesion (proximal to the target lesion), whereas plaque 4 was the target lesion with a severe luminal narrowing. On ICUS, both plaques were classified as intermediate lesions. Area stenosis was 73% in plaque 3 and 93% in plaque 4. These plaques were clearly detectable by MSCT, and density measurements revealed 83 (17) HU for plaque 3 and 51 (19) HU for plaque 4.

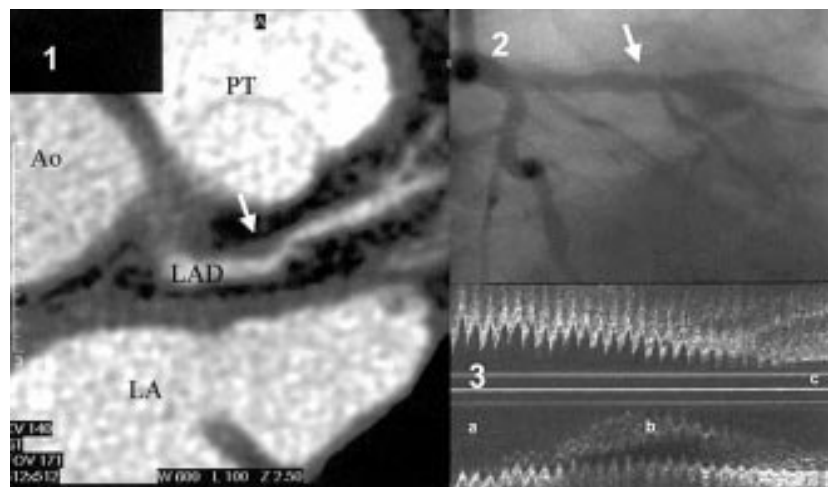


Figure 1 Soft plaque with a lipid core visualised by multi-slice computed tomography (MSCT), coronary angiography, and intracoronary ultrasound (ICUS). (1) MSCT: axial slice visualising the left anterior descending artery and a soft plaque (arrow). (2) Coronary angiography: visualising the soft plaque (arrow) as a minor vessel wall alteration. (3) ICUS: longitudinal view of the left anterior descending artery, visualising the soft plaque. a, vessel lumen; b, soft plaque with a lipid core; c, ultrasound catheter with guiding wire inside. Ao, aorta; PT, pulmonary trunk; LA, left atrium; LAD, left anterior descending artery.

Plaque 3 was correctly classified as a moderate to severe lesion, and plaque 4 as a severe lesion (table 1).

In patients 5 and 6, calcifications could already be detected in projection on the proximal LAD by angiography. Plaque 5 was proximal to the angiographically detectable severe target lesion, and was classified as a moderate lesion. Plaque 6 was the target lesion with severe luminal narrowing. On ICUS, both plaques were classified as calcified lesions. Lesion severity was 53% (arc of calcification of 185°) in plaque 5 and 93% (arc of calcification of 95°) in plaque 6. These plaques were clearly detectable by MSCT, and density measurements revealed 489 (372) HU for plaque 5 and 423 (111) HU for plaque 6. Plaque 5 was classified as an intermediate lesion, and plaque 6 as a severe lesion (table 1).

Non-invasive coronary angiography with good image quality can be performed by the use of the new generation of conventional spiral computed tomography scanners with multi-slice technology. Because of improved temporal and spatial resolution,² this new modality seems to provide information on coronary atherosclerosis which could only be achieved by ICUS. MSCT seems to allow not only for the non-invasive detection of coronary lesions, but also for the accurate differentiation of plaque morphology. Since intracoronary soft plaques might also be detected, which are known to be prone to rupture inducing acute coronary syndromes,^{1,5} MSCT holds promise to allow for non-invasive risk assessment in patients with known or suspected coronary artery disease.

STEPHEN SCHROEDER
ANDREAS F KOPP*
ANDREAS BAUMBACH‡
AXEL KUETTNER
CHRISTIAN GEORG*
BERND OHNESORGE†
CHRISTIAN HERDEG
CLAUS D CLAUSSEN*
KARL R. KARSCH‡

Department of Internal Medicine,
Division of Cardiology,
Eberhard-Karls-University Tuebingen
Tuebingen, Germany

*Department of Radiology,
Division of Diagnostic Radiology

Eberhard-Karls-University Tuebingen

†Siemens AG, Medical Engineering, Computed
Tomography,
Forchheim, Germany
‡Bristol Heart Institute,
University of Bristol
Bristol, UK

Correspondence to: Dr Schroeder, Medical Clinic III, University of Tuebingen, Otfried, Mueller Str. 10, 72076 Tuebingen, Germany; Dr.Schroeder@t-online.de

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Effects of pretreatment with verapamil on early recurrences after electrical cardioversion of persistent atrial fibrillation: a randomised study

Atrial fibrillation (AF) is a very common arrhythmia, which increases in prevalence in patients older than 60 years.^{1,2} Over time, it tends to become persistent or chronic, even if no underlying structural heart disease is present.^{1,2} Evidence that AF promotes AF emerges from the fact that the success rate of electrical cardioversion and the maintenance of sinus rhythm are highly dependent on the duration of the previous AF episode.^{3,4} A possible explanation for these epidemiological and clinical observations, apart from the progressive change caused by underlying cardiovascular disease, is the concept of electrical remodelling of the atria: AF itself causes progressive electrophysiological and structural changes to the atria, which promote the initiation or perpetuation of AF.⁵

The phenomenon of "AF begetting more AF" was first described in a goat model. Atrial electrical remodelling induced by AF seemed to develop quickly, to be progressive, and to be completely reversible within one week after restoration of sinus rhythm.⁵ To date, many reports have confirmed the presence of atrial electrical remodelling after short and long term AF or rapid atrial pacing in animal models.⁶⁻¹² In humans, the time course of appearance and reversal of atrial electrical remodelling resembles that seen in goats and dogs.¹³⁻²¹

The mechanism behind this phenomenon has not yet been clarified. There are some indications that intracellular calcium overload plays an important role. In both animal and human models, verapamil administered during rapid atrial pacing or short episodes of artificially induced AF reduces atrial electrical remodelling.^{7,9,12,14,16} By contrast, pretreatment with verapamil results in a shortening of refractory periods in humans and animals with long lasting AF.^{11,18,22,23} Only two studies have found that the use of calcium antagonists or β blockers reduces early recurrences after electrical cardioversion of chronic AF.²¹⁻²⁴

Amiodarone is usually administered as a "last resort" in patients who fail to maintain sinus rhythm despite serial antiarrhythmic treatment.²⁵ Furthermore, concomitant administration of verapamil during amiodarone treatment has been reported to be an independent factor that determines the likelihood of successful electrical cardioversion in patients with persistent atrial flutter/AF.²⁵

The aim of this prospective, randomised study was to investigate whether early recurrences after internal or external electrical cardioversion of persistent AF in patients on amiodarone could be reduced by pretreatment with verapamil.

From July 1998 to May 1999, 189 patients with persistent (> 72 hours) AF were referred to our department to undergo elective electrical cardioversion. One hundred and thirty three patients were on amiodarone or began to take amiodarone at the time of examination. On the basis of exclusion criteria, 33 patients were not enrolled in the study because of the following reasons: treatment with intracellular calcium lowering drugs in 20; mean ventricular rate < 60 beats/min in 6; previous side effects of verapamil in 2; left ventricular ejection fraction < 40% in 5. Thus, 100 patients were randomised in a one to one fashion to receive 120 mg verapamil twice daily in addition to amiodarone for at least four weeks

before and four weeks after electrical cardioversion (group V) or only amiodarone (group C). Patients already on amiodarone went on receiving 200 mg/day; patients who began amiodarone on randomisation received 400 mg/day for four weeks, and then 200 mg/day. Calcium channel blockers (verapamil, diltiazem, and dihydropyridines) and β blockers, excluding sotalol, were defined as intracellular calcium lowering drugs.²¹

All patients gave informed written consent to take part in the study.

On inclusion in the waiting list for elective electrical cardioversion, each patient's clinical and pharmacological history was collected, and physical examination, ECG, chest x ray, and echocardiogram were performed. All patients received oral anticoagulation for at least four weeks before and four weeks after the electrical cardioversion.

Elective electrical cardioversion was planned after four weeks. Meanwhile, AF was confirmed by intermittent ECG.

External electrical cardioversion was performed under general anaesthesia with intravenous propofol or thiopental in fasting patients. Shock was delivered with external paddles positioned in the anterior-apex position connected to an external cardioverter (CardioServ, Hellige Inc, Freiburg, Germany). Initial energy varied from 200-300 J according to the patient's size. If the first attempt at cardioversion failed, shock was delivered in the anteroposterior position at 360 J.

Patients underwent internal electrical cardioversion if previous external cardioversion proved ineffective. Time from unsuccessful external cardioversion to internal cardioversion varied from seven days to many years. Internal electrical cardioversion was performed under deep sedation with 10 mg of intravenous diazepam. A single defibrillation catheter (Alert -EpMedSystem Inc, New Jersey, USA) inserted through the right femoral vein was positioned in the right atrium and in the left or right pulmonary artery. Shock was delivered between electrodes positioned in the right atrium and in the left or right pulmonary artery. The starting energy was 8 J. In the event of failure, shock was repeated at 15 J. Thereafter, positions of the electrodes were changed, and shock repeated at 15 J.

Electrical cardioversion was deemed successful if at least two consecutive sinus beats were recorded immediately after the shock.

Trans thoracic two dimensional imaging and pulsed Doppler echocardiography were

Table 1 Comparison of incidence of dropouts among patients pretreated with verapamil (group V) and not pretreated with verapamil (group C)

	Group V (n=50)	Group C (n=50)	p Value
Spontaneous conversion to sinus rhythm (%)	14	12	1.00
Unsuccessful electrical cardioversion (%)	8	4	0.34
Total (%)	22	16	0.45

performed using Hewlett-Packard Sonos 1500 or 2000 ultrasound machines equipped with 2.5 and 3.5 MHz phased array transducers (Hewlett-Packard Co, Andover, Massachusetts, USA) before AF termination. Left ventricular ejection fraction was determined by calculating the end diastolic and end systolic volumes according to Folland. Left atrial size was measured at end systole in the parasternal long axis views.

ECG was performed six hours, seven days, and 30 days after electrical cardioversion. Only reappraisal of AF with ECG documentation was counted as recurrence.

Continuous variables are presented as mean (SD). Discrete variables are presented as percentages. Analyses were performed according to the intention-to-treat principle. For comparison of groups, continuous variables were tested using two tailed Student's *t* test for unpaired data; discrete variables were tested using the χ^2 test or Fisher's exact test. A probability value of $p < 0.05$ was considered significant.

Fifty patients were randomised to group V, and 50 to group C. Nineteen patients (11 in group V and eight in group C patients, $p = NS$) were excluded from the analysis: 13/100 patients had spontaneous conversion to sinus rhythm (13%); 6/100 patients in whom external electrical cardioversion was unsuccessful refused to undergo internal cardioversion (6%). The incidence of dropouts in the two groups is shown in table 1. One patient (2%) suspended treatment with verapamil owing to adverse events, which appeared during the four weeks before electrical cardioversion. However, according to the intention-to-treat analysis, this patient was included in the final analysis. Thirty nine patients in group V and 42 patients in group C were analysed. Group V and group C patients were comparable in terms of clinical and echocardiographical characteristics (table 2).

Table 2 Comparison of clinical and echocardiographical characteristics of patients pretreated with verapamil (group V) and not pretreated with verapamil (group C)

	Group V (n=39)	Group C (n=42)	P value
Age (years)	65.9 (9.0)	65.3 (9.7)	0.79
Male sex (%)	64	64	0.83
Underlying heart disease (%)			
Coronary heart disease	18	12	0.65
Systemic hypertension	33	23	0.48
Dilated cardiomyopathy	8	7	0.61
Valvular heart disease	10	17	0.32
Cor pulmonale	0	5	0.26
Lone atrial fibrillation	31	36	0.81
Atrial fibrillation relapses (n)	1.5 (1.7)	3.4 (15.3)	0.33
Previous electrical cardioversion (n)	1.5 (1.2)	1.5 (1.9)	0.97
Previous unsuccessful electrical cardioversion (n)	0.5 (0.6)	0.4 (0.7)	0.44
Atrial fibrillation episode duration (days)	276 (8528)	228 (438)	0.77
Digoxin (%)	41	55	0.31
Mean ventricular rate (bpm)	78.5 (19.2)	82.4 (19.0)	0.42
Left atrial size (mm)	48.2 (6.4)	47.7 (6.3)	0.71
Left ventricular end diastolic diameter (mm)	54.9 (6.9)	52.6 (5.2)	0.12
Left ventricular ejection fraction (%)	55.6 (9.1)	56.5 (8.8)	0.66
Internal electrical cardioversion (%)	21	26	0.73

Data are presented as mean (SD), unless otherwise indicated.

AF relapses occurred in 14/81 patients (17%) within six hours of the restoration of sinus rhythm; in 31/81 patients (38%) within seven days; and in 39/81 patients (48%) by the end of the follow up. Among the 39 relapses of AF during the 30 day follow up, 31 (79%) occurred during the first seven days.

A trend toward a higher incidence of relapses of AF in the patients receiving verapamil (group V), although not significant, was seen at each follow up time: 9/39 (23%) *v* 5/42 (12%) within six hours ($p = \text{NS}$), 18/39 (46%) *v* 13/42 (31%) within seven days ($p = \text{NS}$), and 21/39 (54%) *v* 18/42 (43%) ($p = \text{NS}$) within 30 days (fig 1).

The results of this study did not show any favourable effect of pretreatment with verapamil in terms of prevention of early recurrences in patients on amiodarone who underwent electrical cardioversion for persistent AF. On the other hand, our findings confirmed the high incidence of relapses in the first few days after conversion of persistent AF.

In our study, 38% of patients had a relapse of AF within the first week—that is, 79% of all recurrences during the first month after electrical cardioversion. This high incidence of recurrences within a few days of sinus rhythm restoration may be the clinical representation of fibrillation induced electrical remodelling of the atria.^{21, 23} The term electrical remodelling was introduced by Wijffels and colleagues⁵ to indicate the significant shortening of the atrial refractory period, and the reversal of the physiological rate adaptation of the atrial refractory periods that appeared after 2–4 weeks of artificially maintained AF.

After Wijffels, many studies, both in animals and in humans, confirmed the concept of atrial electrical remodelling.^{6–20, 26} This process has been reported to commence within a few minutes of the onset of AF.^{7, 13, 16, 23} The time course of reversibility of electrophysiological modifications that characterise atrial electrical remodelling has been seen to depend strictly on the duration of AF, and to range from two minutes to seven days.^{7, 9, 12, 13, 14, 16, 20, 21, 23, 27} Indirect documentation of recovery from electrical remodelling within seven days of electrical cardioversion for persistent AF (lasting more than one month) is provided by this study.

Many mechanisms have been proposed to explain atrial electrical remodelling. The role of ischaemia, shifts in vagal or sympathetic tone, mechanical stretching of the atrial wall, increase in plasma natriuretic factor, and increase in outward potassium current have not been confirmed.^{5, 7, 12, 28–32} By contrast, cytosolic calcium overload has been suggested as an important mediator of this phenomenon.^{7, 9, 12, 14, 16, 21, 23, 24, 26, 31, 32}

The duration of AF may have implications for the underlying cellular mechanisms involved in the cytosolic calcium overload. Changes in ionic pump activity or phosphorylation of ion channels occur within seconds or minutes after a change in heart rate.^{26, 28} Only if the heart rate remains altered for days do processes other than metabolic adaptation come into play. Down regulation of the L type calcium channel and of Ca²⁺-ATPase has been reported after three months of AF.³² Thus, in a later phase of AF, the decrease in the L type calcium channel and in calcium uptake by Ca²⁺-ATPase further contributes to the cytosolic calcium overload and to the shortening of the action potential duration.³² After several weeks of AF, structural changes may contribute to the maintenance of AF.³³

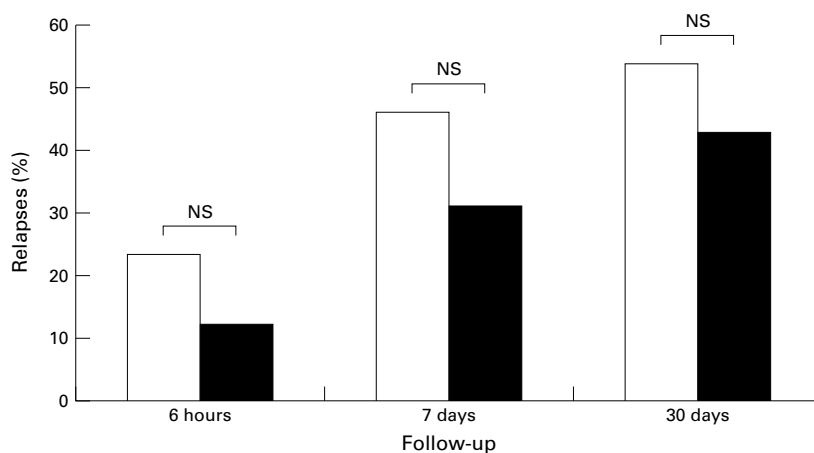


Figure 1 Cumulative incidence of relapses of atrial fibrillation. Open bars, group V (amiodarone + verapamil); solid bars, group C (amiodarone). NS, not significant.

The increase in mitochondrial size and disruption of the sarcoplasmic reticulum may further increase cytosolic calcium overload.⁶

In experimental studies, pretreatment with verapamil has been reported to blunt electrical and mechanical remodelling after short term AF (from five minutes to 24 hours).^{7, 9, 12, 14, 16, 23, 28} Despite these encouraging findings, there is controversial clinical evidence of a possible role of pretreatment with intracellular calcium lowering drugs in the prevention of electrical remodelling induced by persistent or chronic AF. Historically, calcium antagonists did not seem to exert any effect on AF, apart from controlling the ventricular rate.³⁴ By contrast, a reduced probability of spontaneous termination of AF during infusion of diltiazem or verapamil was reported.^{11, 18, 35} After internal electrical cardioversion of chronic AF, refractory periods were shorter in patients pretreated with verapamil than in those not pretreated²²; moreover, verapamil pretreatment increased the duration of AF in dogs both before and after long term atrial pacing.²³ Pretreatment with diltiazem did not achieve any significant reduction in the incidence of early recurrences after electrical cardioversion of persistent AF in comparison with amiodarone pretreatment.³⁶ Only one small, observational, non-randomised study found that the use of intracellular calcium lowering drugs reduced early recurrences after electrical cardioversion of spontaneous AF.²¹ More recently, a prospective randomised study demonstrated that the administration of oral verapamil combined with propafenone for six days, centred around the cardioversion day, significantly reduced the incidence of early AF recurrences compared with oral propafenone alone.²⁴

In this study we did not find any significant difference in terms of incidence of early relapses of AF between patients pretreated with verapamil and patients not pretreated. On the contrary, a trend toward a higher incidence of relapses of AF in the patients pretreated with verapamil was observed at each follow up time. Our findings are supported by data from Lee and colleagues,²³ but contrast starkly with those of De Simone and associates.²⁴ It is not easy to explain this discrepancy. The only clear difference between the two studies is the cumulative incidence of recurrences of AF within three months, which is very low in De Simone's study (24%). Patients with such a low risk of AF recurrences may have different clinical and electrophysiological characteristics from

our study group, which presented a cumulative rate of AF relapses of 48% within 30 days.

There are, however, some possible explanations for the different effects of intracellular calcium lowering drugs on the prevention of AF induced electrical remodelling after brief or long lasting episodes of spontaneous or induced AF. Pretreatment with intracellular calcium lowering drugs may prevent cytosolic calcium overload related to ionic mechanisms which account for the electrical remodelling that occurs during the first hours of AF.^{26, 28} However, after weeks or months of AF, as in our study patients, changes in the gene expression of Ca²⁺ handling proteins and intracellular structural modifications further contribute to the cytosolic calcium overload, in a manner that cannot be affected by pretreatment with intracellular calcium lowering drugs.^{6, 31–33}

As verapamil was administered in a slow release preparation of 120 mg twice a day, serum drug concentrations over 24 hours may have been less stable than if 80 mg had been given three times a day.

Plasma concentrations of amiodarone and desethylamiodarone were not controlled at the moment of electrical cardioversion. Patients who started amiodarone on randomisation with a loading regimen of 400 mg/day for four weeks might have had lower plasma concentrations than those already on amiodarone. However, this bias should not have affected the result of the study, as the prevalence of patients who began amiodarone on randomisation was exactly the same in both groups (56% in group V and 57% in group C).

About 50% of patients in both groups were on digoxin. This may have affected the outcome, as digoxin itself may delay recovery from electrical remodelling of the atria after 24 hours of rapid atrial pacing.^{36, 37} However, there are no data on the effects of digoxin after long term AF. Nevertheless, there was no significant difference in the percentage of patients pretreated with digoxin between group V (41%) and group C (55%).

Among the multiple direct and indirect effects of amiodarone, a calcium channel blocker effect has been reported after acute administration.³⁸ Thus, in our study, the benefit of pretreatment with verapamil might have been obscured by the reduction in intracellular calcium induced by pretreatment with amiodarone. However, the calcium channel

blocker effect of amiodarone has been demonstrated only after acute intracellular or intravenous administration; many effects of intravenous amiodarone are absent after chronic oral administration.³⁹ Moreover, the prolongation of action potential duration induced by amiodarone is likely to elicit an opposite effect on cytoplasmic calcium content.⁴⁰ For this reason amiodarone is not usually included among calcium lowering drugs.²¹

Our findings confirm the high incidence of relapses in the first few days after conversion of persistent AF. However, pretreatment with verapamil did not show any favourable effect in terms of prevention of early recurrences in patients on amiodarone who underwent electrical cardioversion for persistent AF.

EMANUELE BERTAGLIA
DANIELE D'ESTE
ALBINO ZANOCCO
FRANCESCA ZERBO
PIETRO PASCOTTO
*Department of Cardiology,
Ospedale Civile,
Mirano (Vénice),
Italy*

Correspondence to: Dr Emanuele Bertaglia, Via Ca' Rossa, 35, 30173 Mestre (VE), Italy; ulss13mir.card@tin.it

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