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Arrhythmia post heart transplantation

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Abstract

A variety of arrhythmias can occur after heart transplantation (HTx). Hearts selected to be donated for HTx should be in good condition and generally beat in sinus rhythm (SR). Absence or loss of SR after HTx can be due to any reason and can lead to serious hemodynamic problems. Ischemia reperfusion injury, unbalanced serum electrolytes and re-warming of cold myocardial tissue are known to initiate arrhythmia during the period of reperfusion after implantation of the heart graft. An important cause of arrhythmias after HTx is the possible rejection reaction, which often prompts supraventricular arrhythmias. Subsequent to the initial course after HTx operation transplant vasculopathy can cause arrhythmias of all kinds. The post-HTx effects of some antiarrhythmic substances such as amiodarone administered preoperatively are at present under discussion as possibly being associated with an increased risk for mortality.
A survey of patients' data from the Deutsches Herzzentrum Berlin (DHZB) showed that continuous SR is accompanied by favorable course after HTx. Absence of SR or its loss predicts organ failure. Significant risk factors for cardiac graft failure were found to be associated with the preoperative condition of recipients and donors as well as with the operative procedures and the respective postoperative courses. Of these risk factors three were prominently associated with cardiac graft failure: absence or loss of SR initially after HTx operation, donor age over 30 years and previous thoracic operation of the recipient. Antiarrhythmic medication regulates cardiac rhythm. We examined the hypothesis whether preoperatively administered antiarrhythmic medication influences post-HTx cardiac rhythm and function due to loading of the recipient's body with an antiarrhythmic substance. The examination of the DHZB data showed that medication for antiarrhythmic purposes in patients waiting for HTx is without influence on the occurrence or continuation of sinus rhythm or on the incidence of arrhythmia after HTx. No preoperatively administered antiarrhythmic substance was associated with postoperative arrhythmia or with cardiac graft failure.

Key words: heart transplantation, sinus rhythm, arrhythmia, cardiac graft failure, cardiac graft function, risk factor, medication, prognosis

Background

Healthy hearts beat in sinus rhythm (SR) (1). Absence of SR is often an early sign of incipient heart disease (2-5). Loss of SR is mostly caused by ischemia or chronic heart failure (CHF) (4,5). Before the onset of antiarrhythmic medication myocardial ischemia should be excluded or treated by reperfusion (6,7).

Hearts to be donated to a recipient waiting for heart transplantation (HTx) should be in good condition in order to fulfil their mission of enabling a long lasting healthy cardiac life for the recipient suffering from cardiac failure with his or her native heart. Most of the harvested hearts beat in SR (8-15). A cardiac rhythm different from SR has to be evaluated to exclude a serious underlying cardiac disease.

Absence or loss of SR after HTx can arise for many reasons (16-22). In the literature different causes mentioned are ischemia, rejection, infection, organ failure, imbalance of electrolytes, anemia, medication, intoxication and others (15,23-28). During the postoperative course after HTx a serious problem can give rise to arrhythmia and subsequently the intention to treat the pathologic cause (29,30). On the other hand the cause-and-effect chain can be reversed to use arrhythmia after HTx as a prognostic marker for future impeding events (20,28,31-38). Most of these reports raise concerns about bradycardia associated with impaired prognosis after HTx and recommend a low threshold for permanent pacemaker (PM) placement. A few studies focus on sinus node dysfunction (SND) early after HTx and find conflicting power for prognosis (18,39). Concerning the initial time course after HTx there is a relative paucity of data about SND and arrhythmia, their prevalence, pathophysiology, impact on prognosis and long-term significance.

HTx is the destination therapy for end-stage CHF (11,22,40-43). Data from the registry of the International Society of Heart and Lung Transplantation (ISHLT) (9) and from international transplant centers show a survival rate of 70 to 85 % for the first year and 60 to 75 % for the first five years after HTx (10,12,13,44-46). During the first year after HTx the highest incidence for serious adverse events (SAE) occurs within the first 30 postoperative days (POD) (47). To prevent SAE a prognostic approach for detecting impeding SAE is desirable. Cardiac graft failure is a possible complication after HTx (9,10,48-51). The occurrence of arrhythmia could possibly be used as a prognostic tool.

Arrhythmia means hemodynamic compromise. This can grow to become a serious problem for patients whose hemodynamics is dependent on marginal cardiac function. Only the optimal synergy of atrial and ventricular function provides the best possible cardiac performance in terms of diastolic filling, additional filling of the ventricles powered by atrial contraction and, finally, systolic cardiac output driven by optimally preloaded ventricles. Every arrhythmia will disturb this nearly perfect evolutionary design of two successively working pump chambers. Therefore every arrhythmia is of diagnostic and therapeutic importance for patients on the edge of hemodynamic deterioration. The margin of this hemodynamic border approximates quite often in the initial stage of the post HTx period.

To focus on arrhythmia, its hemodynamic consequences and medical treatment during the initial period of the first 30 POD after HTx we surveyed publications in the medical literature and the follow-up data of the first post-HTx year from patients of the Deutsches Herzzentrum Berlin (DHZB).

Material and methods

Literature was surveyed with the search engine for PubMed of the U.S. National Library of Medicine of the National Institutes of Health using the keywords HTx, SR, arrhythmia, SND, prognosis, cardiac graft failure, hemodynamic deterioration, etiology, pathological cause, diagnostics and therapy.

In studying the DHZB data, we investigated perioperatively and for one year 150 consecutive patients who underwent HTx in our institution between July 1998 and December 2000. Data concerning hemodynamics, cardiac rhythm and medication were collected from donors and recipients. Additionally, recipients' medical records describing general condition, SAE and cardiac and non-cardiac organ function were examined. We focused on the occurrence of arrhythmias, their origins and consequences, their diagnosis and treatment, and calculated logistic regressions for causal relations. Per case more than 450 factors were considered as possible markers of prognosis of outcome.

The demographics and diagnoses of the heart donors and HTx recipients are given in tables 1 and 2. Of the 150 recipients 14 were children, two of them babies 4 and 6 weeks old. Five of the 150 recipients underwent repeated HTx. Thirty-two of the 150 recipients were supported by a mechanical ventricular assist device before HTx.

The technique of harvesting the donated hearts, HTx operation and the concept of immune suppression are described in appendices A to C. Table 3 presents the intraoperative time periods.

Publications and results from the DHZB

Ischemia reperfusion injury, imbalance of electrolytes and re-warming of cold myocardial tissue are known to initiate arrhythmia during the period of reperfusion after implantation of the transplant graft (11, 12, 14, 15, 25, 52). The impaired diastolic compliance post-HTx is counterbalanced by the increased heart rate to compensate the decreased Frank-Starling effect (53,54). To achieve satisfactory hemodynamics the heart

Table 1: Demographics and diagnoses of the 150 donors

Gender	99 male (66 %)	51 female (34 %)			
	mean	minimum	maximum	median	
Age of all donors (years)	40	0.1	66	44	
Female donors' age (years)	41	0.1	66	45	
Male donors' age (years)	40	4	64	44	
Body height (cm)	171	55	197	175	
Body weight (kg)	74	4	140	75	
BMI (kg/m^2)	24.5	11	39	24	
Diagnoses for brain death					
Cephalic trauma	Subarachnoidal bleeding	Intracerebral bleeding	Hypoxia	Brain tumor	Apoplexia
55 (37 %)	42 (28 %)	36 (24 %)	9 (6 %)	5 (3 %)	3 (2 %)

BMI denotes body mass index, which is calculated from the quotient of body weight (kg) and the square of body height (m^2).

Table 2: Demographics and diagnoses of the 150 recipients

Gender	119 male (79 %)	31 female (21 %)		
	mean	minimum	maximum	median
Age of all recipients (years)	47	0.2	67	52
Female recipients' age (years)	35	0.2	64	39
Male recipients' age (years)	50	2	67	55
Body height (cm)	169	54	190	173
Body weight (kg)	69	3	110	73
BMI (kg/m^2)	23.6	11	34	24
Diagnoses for HTx	IDCM	CAD	on HTx	other
	99 (66 %)	36 (24 %)	5 (3 %)	10 (7 %)
Additional non-cardiac diagnoses of the recipients				
Previous thoracic operation	Previous cardio-pulmonary resuscitation	Diabetes mellitus*	Arterial hypertension*	Renal dysfunction*
50 (33 %)	14 (9 %)	19 (13 %)	21 (14 %)	51 (34 %)

BMI denotes body mass index, which is calculated from the quotient of body weight (kg) and the square of body height (m^2). IDCM, CAD and "on HTx" denote idiopathic dilated cardiomyopathy, coronary artery disease and status after first HTx with need for a second HTx (re-HTx), respectively. "Other" diagnoses for HTx summarizes seven patients suffering from congenital vitia, two patients suffering from aortic valve vitia and one patient suffering from hemosiderosis due to major β-thallassemia. *permanently applied medication.

Table 3: Intraoperative time periods (minutes)

	mean	**minimum**	**maximum**	**median**
Operation in toto	503	235	2575	398
On CPB	308	116	2000	236
Aortic cross clamp	61	35	220	55
Ischemia	187	55	323	195
Reperfusion	222	54	1430	163

CPB denotes cardiopulmonary bypass

rate is often upregulated from 90 beats per minute (bpm) due to vagotomy up to 130 bpm by external PM stimulation or the intravenous (i.v.) administration of orciprenaline, theophylline or epinephrine (55). The administration of theophylline for bradycardia shortly after HTx is known to prevent the need for permanent PM implantation (23,56).

Frequent arrhythmias during the initial time period after HTx operation are bradycardiac sinus, atrial-ventricular (AV) node regulated or rhythms with supraventricular origin (18,23,26,57). They can result in tachycardia due to the operation with cardiopulmonary bypass, complete denervation of the harvested heart or administration of hemodynamically active medication (26). The biatrial operation technique of Norman Shumway, Richard Lower and RC Stofer (22,58), by which both atria of the donor and recipient are anastomosed, can cause supraventricular arrhythmia due to ischemia or injury of the sinus node or the changed geometry of the atria (14,57).

An important reason for arrhythmia after HTx is the rejection reaction, often manifesting in supraventricular form (59). Following the initial course after HTx operation, CAD (6,60) and transplant vasculopathy (TVP) (61-65) can cause arrhythmias of all varieties (19).

In treating arrhythmias after HTx the fact of denervation has to be taken into account. The parasympathetic and sympathetic efferentia are cut. Drugs such as atropine that act on these sites in the native heart are without effect. Digitalis loses its effect on the acceleration of the AV node. Nifedipine does not show any reflex tachycardia. The sympathetic denervation of the harvested heart initiates an upregulation of the adrenoreceptors, resulting in hypersensitivity to catecholamines and the adrenoceptor-blocking effects of b-blockers. Neural re-innervation of the heart has been described after long-term course post HTx (21,66-69).

In the medical literature one of the most frequently described antiarrhythmic substances used at HTx is amiodarone, a class III drug according to the classification of Vaughan and Williams. After preoperative administration it can be traceable in the transplanted cardiac tissue for three months after HTx (70). The post-HTx effects of amiodarone administered preoperatively are still under discussion: some studies found an increased risk for mortality (71,72), others did not (73-75).

All hearts harvested for HTx at the DHZB during the above mentioned study period were beating in SR. None of the donors had a severe cardiac disease, an arrhythmia or hemodynamic compromise with cardiac cause. All donated hearts were implanted in cardioplegic arrest (see appendix A for details).

The heart rhythms intraoperatively after the opening of the aortic clamp (for HTx operation technique see appendix B), at the end of the operation, directly after the HTx operation and arrival on the intensive care unit (ICU) and at the end of the operative day are shown in tables 4 and 5. The time of reperfusion was set as half of the ischemic time at the minimum or was marked by the onset of SR.

Based on the directly postoperative cardiac rhythm (91 patients in SR) 43 patients (29 % of 150) developed a stable SR without its loss. An intermittent SR was recorded for 105 patients (70 %) for the first two postoperative weeks (POW). Six patients (4 %) initially had SR, but lost it after the first two POW. Of the total of 150 patients, 43 (29 %) never developed a stable SR; 38 of these suffered cardiac graft failure during the postoperative course.

Loss of SR over a length of four days occurred in 33 patients (22 %), over a length of 5 to 14 days in 16 patients (11 %), and for longer than 14 days in 19 patients (13 %). Forty-three patients (29 %) never lost their SR. Thirty-nine of these kept their satisfactory cardiac graft function for one year (until the end of the study recordings); four of these 43 patients developed cardiac graft failure.

The pathological reason for the loss of SR could not be clearly detected in 61 patients (41 %); in 40 patients (27 %) cardiac graft

Table 4: Cardiac rhythm in chronological correlation to HTx operation

	Opening aortic cross clamp	At weaning from CPB	At the end of HTx operation
SR	18 (12 %)	115 (77 %)	91 (60 %)
Ventricular fibrillation	93 (61 %)	-	-
AV Block III	24 (16 %)	11 (7 %)	20 (14 %)
Ventricular rhythm	8 (6 %)	17 (11 %)	32 (21 %)
Asystole / PM dependency	7 (5 %)	7 (5 %)	7 (5 %)

AV, CPB and PM denote atrio-ventricular, cardiopulmonary bypass and pacemaker

Table 5: Cardiac rhythm during post HTx course

	End of OP day	POD			POW			POM		POY
Rhythm		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**6**	**1**
SR	83	67	69	68	78	85	94	100	101	97
Bradycardia	8	8	8	5	1	0	0	0	0	0
Instable SR	14	16	20	17	12	9	5	1	0	0
Supraventricular tachycardia	5	3	2	0	1	1	4	1	0	0
Ventricular rhythm	21	23	20	19	8	6	3	4	1	4
Atrial fibrillation	2	6	13	23	22	18	9	4	2	0
Asystole / PM dependency	12	11	4	3	4	1	1	1	1	0
VES	3	11	4	3	2	1	1	2	0	0

POD, POM, POW and POY denote postoperative day, month, week and year, respectively. PM and VES = pacemaker and ventricular extrasystole, respectively

failure was diagnosed as the reason for SR loss, and in 6 patients (4 %) graft rejection was found. Other causes for loss of SR were hyperthyroid gland activity, rhabdomyolysis with hyperkalemia and sepsis in 6 patients (4 %).

A stable SR developed in 107 patients (71 % of 150): in 48 patients (32 % of 150) of these within the first two POD, in 26 patients (17 % of 150) between POD 3 and 7, in 9 patients (6 % of 150) between POD 8 and 14, in 16 patients (11 % of 150) between POD 15 and 30, and in 8 patients (5 % of 150) later than the first postoperative month (POM). Electrical cardioversion was performed in 21 patients, in most of them several times. Permanent PM stimulation was necessary in 7 patients (5 %). The prevalence of arrhythmia during the first year after HTx is given in table 6.

Patients whose hearts beat in SR during the post-HTx period had a heart rate of 90 bpm or higher at rest. The increased rate during the initial period post HTx is caused by vagotomy (54). During exercise the heart rate further increased after a latency time due to excreted and circulating adrenergic hormones (29, 53, 76, 77).

Type of arrhythmia	n	%*
AV Block III	26	17
SVES	26	17
SVES plus AV Block III	10	7
Asystole / PM dependency	7	5
Complex VES	30	20

AV, PM, SVES and VES denote atrioventricular, pacemaker, supraventricular extrasystole, ventricular extrasystole, respectively. *percentage of the 150 patients of the DHZB survey

Table 6: Prevalence of arrhythmia post HTx operation of the 150 recipients

Type of cardiac rhythm	n	%*
SR	75	50
SR tachycardia	11	8
Atrial fibrillation	50	33
PM stimulation	14	10

*percentage of the 150 patients of the DHZB survey

Table 7: Prevalence of variety of cardiac rhythm pre HTx operation of the 150 waiting recipients

Table 8: Prevalence of antiarrhythmic medication pre and post HTx operation

	Pre HTx		Post HTx	
	n	%*	n	%*
Amiodarone	48	32	14	10
b-blocker	57	37	-	-
Digitalis	116	77	12	8
Lidocaine	-	-	13	9
Magnesium	13	9	3	2
Orciprenaline	-	-	3	2
Propafenon	2	1.4	-	-
Sotalol	3	2	1	0.7
Theophyllin	-	-	23	15
Verapamil	2	1.4	6	4

*for percentage of the 150 patients of the DHZB survey

The preoperative cardiac rhythm showed a variety of SR, sinus bradycardia and tachycardia, atrial fibrillation and PM stimulated heart beat; their prevalence is given in table 7. The antiarrhythmic substances administered pre- and postoperatively are listed in table 8.

Based on these data we tested three hypotheses (A - C):

A Cardiac rhythm after HTx operation is correlated with the cardiac graft function and the clinical outcome.

B Demoscopic and clinical data of heart donors and recipients can be used to as-

certain risk factors for cardiac graft failure after HTx operation.

C Preoperatively administered anti-arrhythmic medication influences the perioperative cardiac rhythm and function.

Ad A

We tested the hypothesis that the presence and continuation of sinus rhythm (SR) parallel a favorable post-HTx course and are prognostic markers for good cardiac graft function. In terms of the occurrence and continuation of SR after HTx, five groups of recipients were formed:

I) SR after HTx and stable SR until POD 30
II) SR after HTx but intermittent loss of SR between POD 1 and 30
III) no SR after HTx but development of stable SR before POD 30
IV) SR after HTx but persistent loss of SR between POD 1 and 30
V) no SR by POD 30.

The correlation between the occurrence and duration of SR/arrhythmia after HTx and cardiac function of the recipients is given in table 9. At the end of the HTx operation SR was present in 91 patients (groups I, II, IV), 43 of whom (group I) showed continuous SR until POD 30 and had no cardiac graft failure after one year. Forty-three patients (groups IV and V) did not develop stable SR; 35 of these (81 %) developed cardiac graft failure. By POD 30, 100 patients had stable SR. Three of these (3 %) developed cardiac graft failure between POD 31 and the end of the first POY. Of the 12 patients with inconspicuous hemodynamics without stable SR at POD 30, 7 (58 %) developed cardiac graft failure between POD 31 and the end of the first POY. Continuous SR is accompanied by favorable course after HTx (78). Absence of SR or its loss predicts organ failure.

Ad B

Cardiac graft failure is a possible complication after HTx. To ascertain risk factors with statistical relevance for cardiac graft failure after HTx the demoscopic and clinical data of heart donors and recipients were examined. In univariate analysis with the Mantel-Haenszel chi-square test significant risk factors for cardiac graft failure were found to be associated with the preoperative condition of recipients and donors as well as with the operative procedures and the respective postoperative courses, as listed in table 10 (79). In multivariate analysis for logistic regression of the risk factors listed in table 10 three were prominently associated with cardiac graft failure: absence or loss of SR initially subsequent to HTx operation, age of donor older than 30 years and previous thoracic operation of the recipient (79), as shown in table 11.

Ad C

Antiarrhythmic medication regulates cardiac rhythm. We examined the question of whether preoperatively administered antiarrhythmic medication influences post-HTx cardiac rhythm and function due to loading of the recipient's body with an antiarrhythmic substance. Therefore, the perioperatively administered antiarrhythmic medication was recorded and evaluated for a correlation to the postoperative course in terms of the oc-

Table 9: Correlation of SR/arrhythmia and cardiac graft function after HTx

Group	**I**	**II**	**III**	**IV**	**V**
Number	43	37	27	11	32
GOOD (%)	100.0	97.3	96.3	27.3	15.6
FAILURE (%)	0.0	2.7	3.7	72.7	84.4

GOOD and FAILURE denote satisfactory graft function and cardiac graft failure, respectively. For characteristics of groups I - V see text ("Results from the DHZB")

Table 10: Significant risk factors for cardiac graft failure

Recipients	previous thoracic operation, previous VAD implantation, higher age, type of cardiac disease leading to HTx
Donors	higher age, time of treatment on ICU, duration of mechanical ventilation before harvesting of the heart
HTx operation	occurrence of SR after release of aortic clamping, time of total operation, time of CPB, time of aortic clamping, time of reperfusion on CPB
Postoperative course	absence or loss of SR after HTx, need for mechanical hemodynamic support, catecholamines and diuretics, duration of stay on ICU, duration of mechanical ventilation, onset and progress of mobilization, occurrence of sepsis or pneumonia

CPB, ICU and VAD denote cardiopulmonary bypass, intensive care unit, ventricular assist device

Table 11: Multivariate logistic regression on risk factors

Risk factors	**p-value**	**Odds ratio**	**95 % confidence interval on odds ratio lower/upper range**	
Absence of SR or its loss in initial postoperative course	< 0.001	6.2	2.5	15.4
Donor age > 30 years	0.024	4.7	1.2	18.0
Previous thoracic operation of the recipient	0.003	3.9	1.6	9.5

currence of arrhythmia, cardiac graft function and postoperative antiarrhythmic medication (see table 8) (80).

The percentage of patients who did or did not receive preoperative anti-arrhythmic medication while waiting for HTx, their postoperative cardiac rhythm and the number with satisfactory cardiac graft function or cardiac graft failure are given in table 12. The comparison shows no detectable correlation between the presence or absence of preoperative antiarrhythmic medication and the postoperative occurrence of arrhythmia nor between the different classes of substances of preoperatively applied antiarrhythmic medication nor a correlation to the stability of SR during the post HTx period nor to cardiac graft failure or satisfactory graft function. The hypothesis was therefore negated that there could have been an influence of preloaded antiarrhythmic medication in the body of the recipient waiting for HTx on the cardiac graft function during the post-HTx course.

Comment

Arrhythmia is well recognised after HTx (18-20,23,26,30-32,37,38,55-57). The establishment of SR is the "intention to treat" for optimizing cardiac graft function and hemodynamics (18,26,29,37,54,76,77,81-83). This can become a pivotal challenge in patients with severely impaired hemodynamics due to marginal cardiac function (32). The SR accounts for a fifth to a quarter of the power of cardiac output. Absence of SR can initiate the formation of thrombi and result in emboli with ischemic consequences, can exaggerate ventricular arrhythmia and start life-threatening ventricular tachycardia or can develop bradycardia or even asystole (1,10,84,85). Therefore the treatment of hemodynamically

Table 12: Correlation of postoperative cardiac rhythm, postoperative cardiac graft function and preoperative anti-arrhythmic medication

Postoperative cardiac rhythm and function/ preoperative medication	Sinus rhythm	AV block	Supra-ventricular arrhythmia	Intermittent supra-ventricular arrhythmia and AV block	Asystole	Ventricular arrhythmia
Number	43	29	28	11	8	31
GOOD / FAILURE (%)	100 / 0	86 / 14	93 / 7	100 / 0	50 / 50	13 / 87
48 / 102 pts on / wo amiodarone (%)	25 / 28	25 / 19	16 / 20	3 / 9	4 / 4	27 / 19
57 / 93 pts on / wo -blocker (%)	27 / 27	19 / 22	25 / 15	8 / 7	4 / 5	17 / 24
116 / 34 pts on / wo digitalis (%)	27 / 26	19 / 29	21 / 13	7 / 10	5 / 3	22 / 19

GOOD and FAILURE denote satisfactory graft function and cardiac graft failure, respectively.
"on" and "wo" denote the percentage of patients (pts) on (on) or without (wo) preoperative anti-arrhythmic medication while waiting for HTx.

disturbing arrhythmias is of crucial importance (86-88).

Arrhythmias of differing genesis can occur after HTx (9,31,33,80). Absence or loss of SR after HTx can develop for many reasons and can lead to serious hemodynamic problems (37,49,89). Among other factors, ischemia reperfusion injury (25), imbalance of serum electrolytes and re-warming of cold myocardial tissue (15) are known to initiate arrhythmia during the period of reperfusion after implantation of the donated heart (14). Importantly, graft rejection may lead to arrhythmias, especially supraventricular arrhythmias after HTx (20). In the later course after HTx, CAD (6,60) and TVP (61-65) can also cause arrhythmias. The post-HTx effects of some antiarrhythmic substances like amiodarone administered preoperatively are under discussion for a possibly increased risk for mortality (70-75), although our data do not support this hypothesis.

The DHZB's data contain different types of arrhythmias post HTx operation. They occur independently of the cardiac rhythm existing before HTx and of the pre-HTx administration of antiarrhythmic medication. In general, post-HTx arrhythmias are treated following the same rationale as in patients without HTx, i.e. by initially excluding or treating a possible imbalance of serum electrolytes, a possible ischemic origin of the arrhythmia, and a suboptimal cardiac pre- and afterload, with or without antiarrhythmic medication (12,13,42,90,91).

Arrhythmia after HTx can be used as an early prognostic marker for future impending events such as cardiac graft failure (78,79) which is one of the most frequent origins of SAE in HTx (10,51). The use of the occurrence of arrhythmia in the later time course after HTx for prognosis is also known (20,28,31-38).

We found that the presence and continuation of SR are associated with a favourable post-HTx course and are prognostic markers for good cardiac graft function. Absence of SR or its loss predicts organ failure. Absence or loss of SR after HTx operation was shown in multivariable logistic regression to be the

strongest significant marker (odds ratio 6.2; confidence internal 2.5 - 15.4) for prognosis of a non-favorable post-HTx course versus continuous SR after HTx. The examination of the DHZB data showed impending cardiac organ failure to be the number one cause for absence of SR after HTx, followed by donor age of over 30 years and previous thoracic operation of the recipient. Most studies concerning the relation between arrhythmia and the prognosis of HTx report on the later follow up after the HTx operation (see "background"). Arrhythmias originating from the higher classes according to the Lown classification are related to an increased risk for SAE and an adverse outcome (7, 28, 50, 51). Surveying the presently available literature shows a relative paucity of data for the initial time phase after HTx of the first 30 POD.

Reports on the effects of amiodarone administered preoperatively on the follow up after HTx present conflicting results. Our data showed that medication for antiarrhythmic purposes in patients waiting for HTx at the DHZB was without influence on the occurrence or continuation of sinus rhythm or the incidence of arrhythmia after HTx (80). No preoperatively administered antiarrhythmic substance was associated with postoperative arrhythmia or with cardiac graft failure.

Appendix A

Technique of harvesting the donated hearts

The donated hearts were approached through a median sternotomy. After occlusion of the superior caval vein and incision of the inferior caval vein the aorta was clamped and cardioplegia was installed by infusion of Bretschneider's HTK solution to the coronary ostia via the aortic root. Cardioplegic volume was 3 L of HTK solution given ice cold over 10 to 15 min at a perfusion pressure of 100 cm H_2O. To prevent ventricular dilatation, the left atrial appendage was additionally incised and the inferior caval vein was kept opened-incised when cardioplegia was initiated. The hearts were excised at the right and left atrial border line according the biatrial technique of Shumway, Lower and Stofer (22, 52, 58) modified by Barnard (40). The excised hearts were physically investigated to exclude abnormal anatomy in terms of vitia and pathologies. They were stored in sterile plastic bags filled with 200 mL of ice cold Bretschneider's HTK solution; the first bag was put into a second bag filled with slush ice and cold saline solution, and then these two bags were put into a third dry bag. This compound of three bags was finally stored in a cool box filled with dry ice for cold storage during transportation.

Appendix B

Technique of the HTx operation

The recipient was connected to normothermic cardiopulmonary bypass (CPB). Excision of the recipient's heart again followed the biatrial technique of Shumway, Lower and Stofer (22, 52, 58) modified by Barnard (40) keeping a wide lateral hem of the recipient's right atrium. Implantation was performed by continuous suture lines of the left and right atria, followed by the pulmonary artery and finally the aorta. After de-airing of the transplanted heart the aortic clamp in the recipient's site was opened for reperfusion. The time of reperfusion on CPB was adjusted to be a minimum of half of the ischemic time, or lasted until the onset of SR or, if SR did not initiate during the minimum time of reperfusion, this was dictated by the surgeon. If ventricular fibrillation occurred, after application of lidocain 100 mg i.v. electrical defibrillation was performed. The applied electrical energy ranged from 6 to 18 joule. Not more than five attempts at defibrillation were undertaken to prevent myocellular damage.

Appendix C

Medication for immunosuppression

Suppression of the recipient's immune system was initiated two hours before HTx oper-

ation by administration of Cyclosporine A and Azathioprine. Intraoperatively Methylprednisolone was given before reperfusion. After the HTx operation, when hemodynamics were stable, polyclonal antimyocyte globuline (ATG) was given to reduce the circulating lymphocytes to 5 % of the preoperative range. For ongoing immunosuppression most patients received triple medication consisting of Cyclosporine A, Azathioprine and Prednisolone. Twenty-one patients (14 %) were treated with Mycophenolat Mofetil instead of Azathioprine.

Appendix D

Documentation and evaluation of SR post HTx operation

Using the operation technique for HTx described in appendix B, i.e. the biatrial technique, the source of SR is the donor's right atrium. The rest of the recipient's right atrium can cause a separate p wave. This electric current is not part of the SR. Investigating the cardiac rhythm with twelve-channel electrocardiogram (ECG) or ECG monitoring, SR was only taken into account if the SR originated in the right atrium of the donor heart with transmission from the donor's right atrium to the donor's ventricles. An additional p wave as a sign of electrically active recipient native right atrium was not regarded as SR.

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