The value of echocardiography in follow-up of human tissue valves in aortic position

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The value of echocardiography in follow-up of human tissue valves in aortic position

De waarde van echocardiografie voor het vervolgen van menselijke weefselkleppen in aortapositie

Proefschrift

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
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aan mijn ouders
in herinnering aan mijn oma

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Introduction & Methods

Chapter 1

Introduction

Historical notes on human tissue valves

The application of human tissue valves for aortic valve or root replacement was introduced during the 1960s. The first successful clinical orthotopic implantation of an aortic allograft was performed by Ross and Barrat-Boyes independently in 1962[1,2]. In 1967 Ross first reported the use of the pulmonary autograft in the subcoronary position to replace a diseased aortic valve[3].

The initial results of implantation of a freshly harvested allograft valve in the orthotopic position were generally good[4]. However, limited donor availability led to the development of preservation methods, like freeze-drying and fresh wet storage at 4 ^{0}C. Concern about the transmission of infection initiated aggressive sterilization techniques: irradiation, highly concentrated antibiotic incubation and glutaraldehyde pretreatment[2,5,6]. Although these methods increased storage time and tissue availability, the clinical durability of the allograft was dramatically inferior to fresh untreated allografts[4]. During this period, reliable artificial heart valves were developed. They were available from the shelf and implantation was less demanding compared to the allograft and autograft implantation. The problems related to preservation and storage, and the development of aortic valve prostheses have delayed a widespread acceptance of human tissue valves.

Improved sterilization methods and adequate harvesting have improved the allograft durability since the early 1970s[7-9]. The development of cryopreservation techniques by Angell and O'Brien has extended the duration of allograft storage in liquid nitrogen[10-12]. The foundation of heart valve banks and the reported good long-term clinical results in the late 1980s have initiated a renewed interest of cardiac surgeons in the use of human tissue valves for aortic valve replacement[8,10-12].

Aortic allografts and autografts have advantages over mechanical and bioprothetic aortic valve prostheses due to their low incidence of endocarditis, thrombo-embolism, anticoagulation-related complications and improved durability compared with bioprostheses. However, their durability is still limited, compared with mechanical prostheses. The limited durability of human tissue valves is the main topic of this thesis.

The durability of human tissue valves

Characteristic for the limited durability of human tissue valves is the development of aortic regurgitation. Human tissue valve regurgitation has a number of mechanisms, such as leaflet degeneration and geometric distortion[13] (Figure 1). Leaflet thinning, tearing and perforation characterize the degenerative leaflet process. Also severe leaflet calcification may occur. Apart from the host tissue response, which alters the structure of the leaflet, there are effects due to a reduction in the intrinsic stretch of the leaflet. This change in mechanical properties of the leaflet is in fact an exaggeration of the normal change of the leaflet tissue resulting from the aging process[14]. In addition, geometric distortion is an important mechanism of valve failure and is related to the implantation technique. The combination of these processes result in the loss of leaflet coaption and progressive aortic regurgitation.

However, the mechanisms of human tissue valve failure are interrelated and are influenced by many risk factors including patient-, valve characteristics and implantation technique. Several studies have shown risk factors like young recipient age[15,16], previous xenograft implantation[16], old donor valve age, large aortic root diameter[8] and the surgeons' learning curve[17,18].

Figure 1 represents the interrelationship between the mechanisms of human tissue valve failure and the risk factors. For example, older donor age as risk factor for allograft failure may be explained by the implantation of a valve with loss of intrinsic stretch. If the size matching of this older donor valve with the host is suboptimal, then geometric distortion, exacerbated by further loss of intrinsic stretch, may reduce quite significantly the leaflet coaption.

The assessment of human tissue valves function

The clinical assessment of human tissue valve function is based on the severity of aortic regurgitation. Regurgitation of bloodflow across the incompetent aortic valve increases filling of the left ventricle and imposes a volume overload. Compensatory mechanisms of the volume overloaded ventricle enable the patient with aortic regurgitation to remain asymptomatic for many years. Symptoms like fatigue, dyspnea, peripheral edema are manifestations of left ventricular failure. Patients may notice palpitations and expericience circulatory sensations, such as prominent pulsations in the neck. These symptoms and the physical findings of aortic regurgitation are caused by the large left ventricular stroke volume with a rapid diastolic runoff[19].

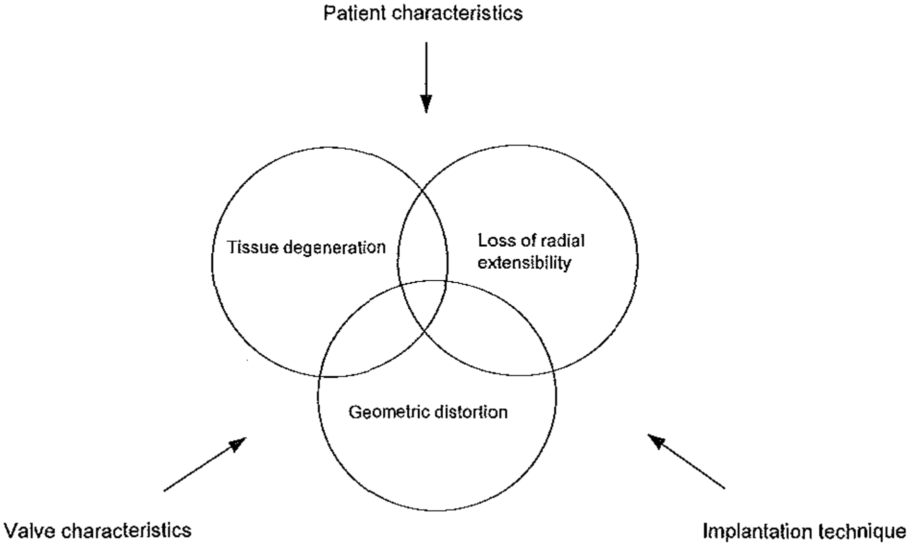

Figure 1. The interrelationships between the overlapping mechanisms of human tissue valve failure and the influence of risk factors.

The peripheral manifestation of this pathophysiologic mechanism include a quick peripheral pulse with a rapid rise in upstroke followed by a peripheral collaps, rhythmic pulsations in the neck and arterial pulsations of the nail beds, reflecting the large stroke volume flowing forward and backward up the aorta. Duroziez' murmur is the systolic and diastolic murmur over the femoral artery, and is a sign of severe chronic aortic regurgitation. Furthermore, the systolic blood pressure is increased and mostly attended by a low diastolic pressure[19]. The pulse pressure also is increased.

Dilatation of the left ventricle displaces the apical impulse inferiorly and laterally. The characteristic auscultatory finding is a high pitched; decrescendo, blowing murmur during the diastolic phase of the cardiac cycle. A ventricular (S3) gallop is frequently heard. The Austin Flint murmur may be heard during the diastolic phase at the apex. The mechanism of this murmur is impingement of the aortic regurgitation jet on the anterior leaflet of the mitral valve, that produces vibration of the leaflet and a functional mitral stenosis. The Austin Flint murmur suggests severe aortic regurgitation. Also a systolic ejection click may be heard and a systolic thrill can be felt precordially due to the large ventricular stroke volume[19].

The changes on the electrocardiogram reflect left ventricular hypertrophy with increased QRS amplitude and ST-T wave depression. The chest roentgenogram shows dilation of the left ventricle and the apex is elongated inferiorly and posteriorly. These classic clinical manifistations of chronic aortic regurgitation, however, may be absent and the diagnosis may be overlooked or the severity underestimated[19]. The end-points for valve failure, reoperation and valve related mortality, are clear but very crude and insensitive measures of valve dysfunction and require a very long follow-up[20].

Echocardiography allows non-invasive evaluation of the process of valve degeneration, and has important consequences for patient counseling and research. Therefore, a prospective, serial, standardized precordial echocardiographic follow-up study was initiated to assess function of human tissue valves and the influence of surgical implantation techniques, patient and valve characteristics on valve function. This thesis is based on the outcome of this study.

Objectives of the study

Valve incompetence is the major cause of allograft or autograft failure[7,8,15-17]. Considering the usefulness of transthoracic color Doppler echocardiography as a method to detect and quantify aortic regurgitation and to assess the process of degeneration during follow-up, we formulated the objectives of this thesis:

- To validate the color Doppler quantification method for aortic regurgitation.
- To identify the sources of variability and reproducibility of the color Doppler quantification method for aortic regurgitation.
- To assess valve pathomorphology and regurgitant jet patterns comparing two surgical implantation techniques; the subcoronary and root replacement technique.
- To determine the influence of the surgeons' learning process on the incidence of reoperation and postoperative aortic regurgitation.
- To determine the severity of postoperative aortic regurgitation and the influence of recipient, donor valve and surgery related factors on late valve function.

Nomenclature

In this thesis an allograft valve is defined as a valve from another individual of the same species. Several authors also use the term "homograft". "Homo-" translates to "equal" or "similar" from the Greek language and "Allo-" translates to "other". The term "homograft" refers to a valve from the same species. Using this term, a differentiation between a semilunar valve from the same patient (autograft) and from another individual is not made. Thus, the term "allograft" refers to a valve from another individual from the same species. It is used in conjunction with the term autograft; a semilunar valve from the same person.

An aortic allograft is usually the aortic root of a donor, that is characterized by a varying length of proximal ascending aorta, the sinuses of Valsalvae, an encircling band of firm fibrous tissue with the leaflets of the aortic valve, a part of the anterior mitral

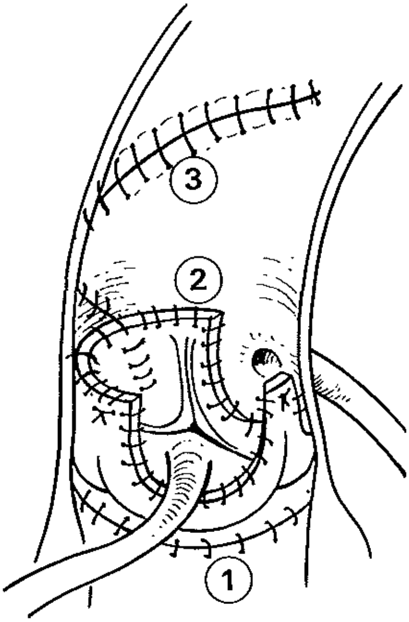

Figure 2

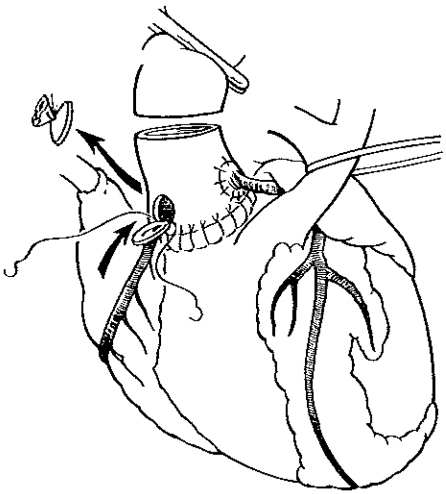

Figure 3

Figure 2. Subcoronary allograft implantation in aortic position (often referred to as the "Ross-method" with scalloping of the left and right coronary sinus. (1) proximal anastomosis, (2) distal anastomosis, (3) closure of the aortotomy.

Figure 3. Aortic root replacement with reimplantation of the coronary ostia.

valve leaflet and adjoining remnants of the muscular left ventricular outflow tract. The pulmonary allograft is defined as the donors' pulmonary root.

The autograft valve is defined as the autologous pulmonary valve inserted in aortic position. The pulmonary valve is replaced with an allograft during the same procedure.

The term subcoronary implies "underneath the coronary arteries" and the subcoronary implantation technique describes the position of a tissue valve implanted below the coronary arteries inside the sinuses of Valsalvae, the aortic annulus and the muscular outflow tract of the ventricle (Figure 2).

The aortic root replacement technique implies resection of the semilunar valve cusps, the sinuses of Valsalvae and a changing amount of proximal ascending aorta, and replacement by an aortic allograft root with reimplantation of the coronary arteries (Figure 3). Usually, the proximal suture line is placed within the annulus of the recipient.

The term inclusion cylinder technique refers to a technique of human tissue valve implantation, where the autograft or allograft root is implanted inside the left ventricular outflow tract and aortic root of the recipient. Since it is often unclear from the literature what is meant by "mini-root replacement" this term should be avoided.

Different preservation techniques are currently available for allograft storage. In this thesis, only cryopreserved aortic allografts were included. Cryopreservation involves freezing the valve at a controlled rate using liquid nitrogen vapours in the presence of cryoprotecting substance. The allograft is stored in the vapour phase of liquid nitrogen (-196 ^{0}C).

Outline of the thesis

Chapter 3 describes the relation between angiography and color Doppler echocardiography for the assessment of the severity of aortic regurgitation. The color Doppler echocardiographic quantification method for the severity of aortic regurgitation, as used during our follow-up study, is validated with the reference method; angiography.

Chapter 4 describes the reproducibility of color Doppler echocardiography for the assessment of aortic regurgitation. The measurements for this quantification method require careful tracing and are subject to considerable variability. An internal validation study is performed to clarify factors determining measurement variability. The advantages of the jet diameter quantification method are discussed.

Chapter 5 describes the pathomorphologic findings and color Doppler jet patterns in a consecutive series of patients after allograft implantation. The possible relation between the incidence of allograft-specific pathology and implantation technique is studied.

Chapter 6 presents a interim report of patients in our center who underwent implantation of a human tissue valve in the aortic position. The influence of the surgical learning curve on the incidence of reoperation and the severity of postoperative aortic regurgitation is studied. The consequences of the grouping of echocardiographic data are discussed.

Chapter 7 presents a follow- up study of all adult patients operated until July 1996, using an aortic allograft or pulmonary autograft in aortic position. The clinical outcome is evaluated and the results of the prospective serial color Doppler echocardiographic study is presented. Special attention is paid to the statistical analysis method, that is used to describe the initial severity of aortic regurgitation and its change during follow-up. The risk factors for human tissue valve failure are discussed.

Chapter 8 presents a discussion about the results from our studies.

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Chapter 2

Methods

Aortic regurgitation

An aortic regurgitant jet is directed towards the left ventricular outflow tract and is produced during the diastolic phase of the cardiac cycle. This regurgitant jet has a high velocity and is surrounded by a region of disturbed flow. The velocity patterns distal to the regurgitant aortic valve in the ascending and descending aorta are frequently of low velocity. The regurgitant fraction is dependent on the size and shape of the valve orifice, the transvalvular pressure drop, the duration of diastole and the diastolic behaviour of the left ventricle. An accurate diagnosis of aortic regurgitation depends on identifying the abnormal regurgitant jet and defining its anatomic location, direction and timing[1,2].

Echocardiographic assessment of aortic regurgitation

Echocardiography is a relative fast and non-invasive tool for the detection and assessment of the hemodynamic severity of aortic regurgitation.

Combined 2D and M-mode echocardiography is useful for monitoring the left ventricular size and function. A diastolic flutter of the anterior mitral leaflet and interventricular septum may be observed on 2D echocardiography. Besides, 2-D echocardiography may identify the anatomic abnormality as the underlying cause of regurgitation. Assessment of its severity can be accomplished by Doppler echocardiographic methods including pulsed-wave mapping, continuous wave and color Doppler imaging[3].

Pulsed-wave mapping is performed by 2D echocardiography. The pulsed-wave signal searchs for a high velocity diastolic jet during placement of a sample volume in the left ventricular outflow tract and left ventricular chamber. The severity of regurgitation has been defined as the depth at which the signal is found in the left ventricle[4,5]. Correlations between pulsed-wave mapping and angiography for semiquantification of the regurgitation severity range from highly significant to rather poor[6,7]. In clinical practice, the pulse-wave method is used for detection of aortic regurgitation in the left ventricular outflow tract and thoracic-abdominal aorta[4].

Continuous-wave Doppler detects aortic regurgitation by visible and audible signals. The audible signals are more conclusive. A positive signal on the monitor starts with aortic closure and a down slope during diastole. The down slope of the signal is a measure of the rate of pressure decay between aorta and left ventricle. A steep down slope is suggestive for severe regurgitation. The t½ p value can be calculated and used to estimate the severity. A t½ p value less than 250 ms is a indication for severe regurgitation[8,9].

However, the assessment of the severity of aortic regurgitation on pulsed-wave or continuous-wave signal underestimates the three-dimensional distribution of regurgitant flow and, hence the severity of the hemodynamic abnormality.

Color Doppler echocardiograpy is very sensitive and specific to diagnose aortic regurgitation and is based on the spatial extent of detected regurgitation. Color Doppler allows immediate visualization of flow disturbance and its pattern into the left ventricle. The regurgitant jet appears as a reverse diastolic flow or as a mosaic flow which is a result of aliasing and turbulence. This diastolic jet originates from the aortic valve.

Different methods are used for the quantification of aortic regurgitation on color Doppler images. They all have their limitations[10]. The semiquantitative assessment of the severity of aortic regurgitation is based on the depth of the regurgitant jet into the left ventricle. This jet length method is largely dependent on systemic afterload and may overestimate the severity of aortic regurgitation[6]. An in vitro model has demonstrated that the jet diameter at its origin is a better predictor of regurgitant volume than the jet length method in different afterload conditions[7].

In a clinical study Perry described that the jet diameter or area of the jet relative to the size of the left ventricular outflow tract is more closely related to the severity of aortic regurgitation than the jet length method. On the basis of a good correlation with angiography, the echocardiographic cross-sectional jet area method is now considered as the best technique[6]. The practical application of the method according to Perry is described in the section Material and Methods of Chapter 4.

Potential limitations of color Doppler imaging is the variation of the jet size for a constant degree of flow which has been shown to relate to the instrument setting. A different instrument setting can lead to variable images, which makes quantitative comparison of aortic regurgitation difficult. Even different instruments with a standardized instrument setting produce variable images. Furthermore, color Doppler echocardiography is highly operator-dependent[11].

Other echocardiographic methods

Regurgitation fraction is an indicator of regurgitation severity that compares regurgitation stroke volume with total forward flow volume. Calculation can made from catherization and Doppler echocardiography. Regurgitant stroke volume is represented by the difference between total stroke volume and forward stroke volume. The total stroke volume is obtained by 2D echocardiographic measurement of the left ventricular outflow area multiplied by the time-velocity integral of the left ventricular outflow measured by pulsed wave Doppler. The forward stroke volume is measured similarly by evaluation of a second, non-diseased valve[2]. This method is not used routinely in clinical practice as a result of technical limitations, measurements errors and is time-consuming[2].

The proximal isovelocity surface area (PISA) method is an example of a color Doppler flow technique which is focused on the flow proximal to the regurgitant orifice. This method identifies a proximal isovelocity surface area by displaying a red-blue aliasing interface. Volume flow rate across the orifice can be calculated as the product of the isovelocity surface area and its corresponding velocity. Dividing the calculated flow rate by orifice velocity gives the effective regurgitant orifice area, a measure for valvular regurgitation. The accuracy of this method for aortic regurgitation is until now not convincing and is experimental[2].

Design of the study

The data described in this thesis relates to patients who underwent an implantation of a cryopreserved aortic allograft or pulmonary autograft in aortic position between December 1988 and July 1996.

The echocardiographic examinations were initially performed with different echocardiographic equipment. Since January 1993 all patients were referred to the echocardiographic laboratory of the Thoraxcenter for a standardized transthoracic examination. The morphology, function and competence of the allografts and autografts were assessed on a Vingmed CFM 750 ultrasound system with identical instruments setting at each follow-up examination. To limit the interobserver variability, only two expericienced technicians performed the echocardiographic studies. Postoperative echocardiographic examinations were scheduled at 6 months, at 1 year and yearly thereafter.

A relational database was developed in Microsoft Access to store pre-, peri- and postoperative data including patient characteristics, valve characteristics and surgical variables. Follow-up data were collected during out-patient visits to the Thoraxcenter or the referring hospital. The echocardiographic data were collected after verification of the quantitative measurements for aortic regurgitation by one observer.

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Validity & Reproducibility

Chapter 3

Validity of angiography and color Doppler echocardiography for the assessment of the severity of aortic regurgitation

Introduction

All human tissue valves have the propensity to fail ultimately after years of adequate hemodynamic function. Thus, early diagnosis of valve dysfunction and quantification of regurgitation are important objectives in patients with an aortic human tissue valve. The severity of valvular regurgitation affects the prognosis of the patient and treatment in case of significant valve dysfunction is warranted. Although angiography remains the reference method for the assessment of aortic regurgitation severity, echocardiography is presently the preferable non-invasive technique for serial evaluation of these patients.

Color Doppler echocardiography has both good sensitivity and specificity for the early detection of aortic valvular regurgitation[1,2,3], but the method is not accurate enough to assess its severity. Semiquantitative assessment is based on measurement of the length of the regurgitant jet projecting into the left ventricle. Alternatively, the jet diameter or the jet area immediately under the aortic valve in relation to the width of the left ventricular outflow tract expressed as a ratio is used to estimate the severity of regurgitation[1,3,4,5].

The purpose of this study is to evaluate the agreement between angiography and color Doppler echocardiographic methods for quantification of aortic regurgitation severity at the Thoraxcenter Rotterdam.

Patients and methods

Patients

The study population comprised 26 patients referred for cardiac surgery, who underwent cardiac catheterization with a contrast injection into the ascending aorta. There were 13 women and 13 men ranging in age from 15.5 to 79.5 years (mean 54.6 years); 7 patients had atrial fibrillation.

Fourteen patients had isolated aortic regurgitation and 6 also had aortic stenosis. Associated mitral stenosis was present in 3 patients, mitral regurgitation in 2 and mixed mitral valve disease in one patient. Five patients scheduled for coronary bypass surgery had light or mild aortic regurgitation, not requiring aortic surgery or replacement. Color Doppler echocardiographic examinations were performed at the time of admission for surgery or prior to surgery. The mean interval between cardiac catheterization and echocardiography was 4 months (range, 0.5 to 8 months). Major clinical or hemodynamic changes did not occur during this interval.

Color Doppler echocardiography

The protocol for precordial echocardiographic examination is described in Chapter 4.

The severity of aortic regurgitation was estimated by the jet length method and the jet diameter or left ventricular outflow tract cross-sectional area ratio method. The length of the regurgitant jet was scored on a scale of 0 to 4; grade 0 being no regurgitation, grade 1 if the jet was limited to the left ventricular outflow tract, grade 2 if the jet was visible extending between the left ventricle outflow tract and halfway the left ventricle, grade 3 if the jet reached halfway into the ventricle, and grade 4 if the jet reached more than halfway into the left ventricle. The depth of the regurgitant jet was reviewed in the parasternal long-, short-axis and in the 4-chamber apical view.

The jet diameter ratio method was performed by measuring the ratio of the maximal regurgitant jet diameter to the systolic left ventricular outflow tract diameter in the parasternal long-axis view[1]. In the parasternal short-axis view the maximal area of the regurgitant jet relative to the left ventricular outflow tract area was measured. During the examination, the imaging plane was angled to demonstrate the maximal regurgitant jet diameter or area just below the aortic valve. Diameters and areas were measured on-line on the video screen from frozen images by planimetry using a trackball. The mean values of measurements in two cardiac cycles were noted. One supervisor reviewed the measurements.

The technicians and supervisor were blinded for the results of the aortic root angiography.

Angiography

In all patients aortic root angiography was performed in the 30° right anterior oblique position. In addition, 15 patients had an aortic root angiography in the 60° left anterior oblique position. The severity of aortic regurgitation was graded on a scale of I to IV by the method of Sellers[7]: grade I, contrast clears the left ventricle with each cardiac cycle; grade II, contrast partially clears the left ventricle with each cardiac cycle; grade III, contrast progressively opacifies the left ventricle to a degree that it almost equals the opacification of the aortic root; grade IV, contrast rapidly opacifies the left ventricle within one or two cardiac cycle, and the opacification exceeds that in the aortic root. The angiograms were interpreted by consensus of two observers. If discrepancy occurred between the two reviewers, the opinion of a third reviewer was decisive.

Statistical analysis

The agreement between the angiographic grading and the color Doppler measurements was analyzed with Spearman's rank correlation test. The level of statistical significance was defined at $p< 0.05$.

Results

Angiography

The severity of aortic regurgitation was graded by angiography as Sellers grade I in 6, grade II in 9, grade III in 8, and grade IV in 3 patients.

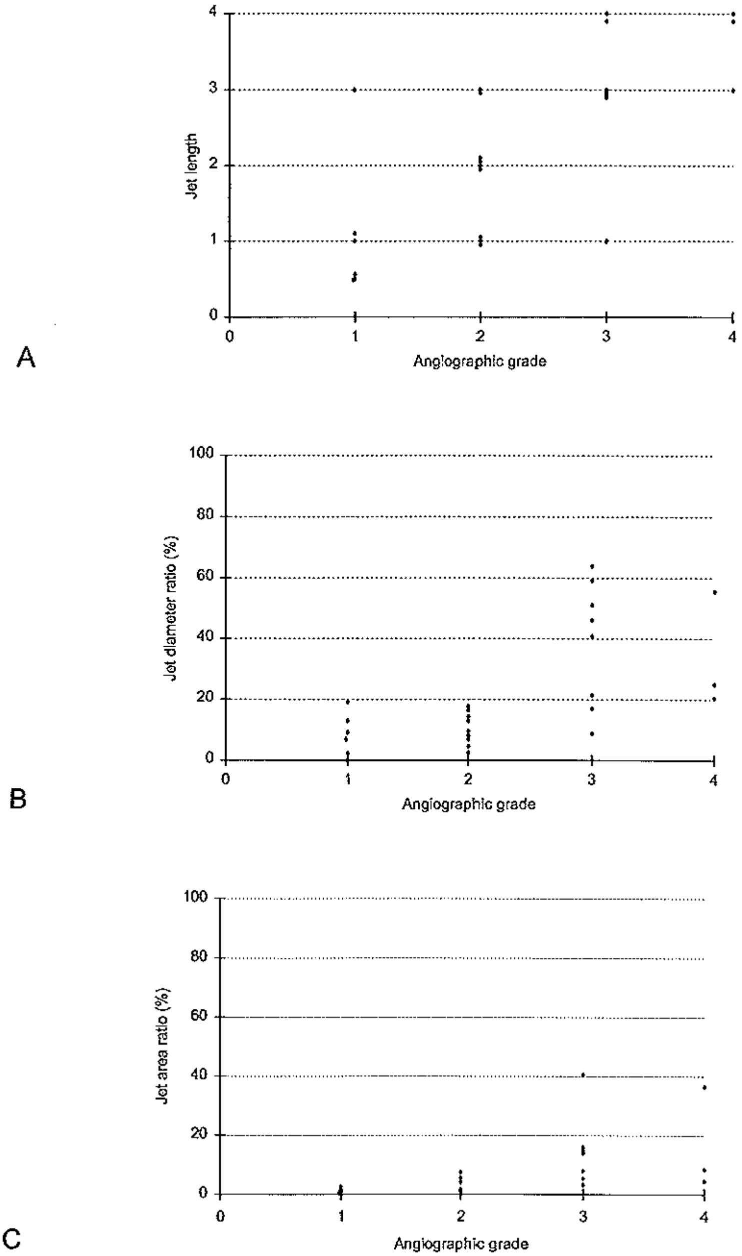

Figure 1. The correlation between the angiographic grade of aortic regurgitation, jet length (A), jet diameter ratio (B) and jet area ratio (C).

Jet length method versus angiographic grading

In all 26 patients the regurgitant jet length was evaluated by echocardiography. A good correlation was found between angiographic grading of aortic regurgitation and the echocardiographic grading with the jet length method; r=0.76 (p<0.01) (Figure 1a). Echocardiographic over-estimation occurred in 5 patients (4 by one grade and 1 by 2 grades) and under-estimation in another 5 patients (4 by one grade and 1 by 2 grades).

Jet diameter method versus angiographic grading

The regurgitant jet diameter and the left ventricular outflow tract diameter in the parasternal axis view could be measured in all patients and its ratio was calculated. Figure 1b illustrates the correlation between the angiographic grade of aortic regurgitation and the jet diameter ratio r=0.73 (p<0.01). It seems that a diameter ratio of 20% may serve as a good discriminator between angiographic grade I and II and the more severe grade III and IV aortic regurgitation. Distinctions between grade I and II aortic regurgitation and grade III and IV turned out to be impossible.

Jet area method versus angiographic grading

In three patients the color Doppler jet area could not be measured because of insufficient quality of the short-axis images. A good correlation between the angiographic grade of aortic regurgitation and the jet area ratio was found; r=0.77 (p<0.01) (Figure 1c). Due to considerable overlap of the calculated jet area ratio's, cut-off values for discrimination between angiographic grade I and II and severe regurgitation grades III and IV were impossible to determine for the jet area method.

Discussion

An accurate method for quantification of severity of aortic regurgitation is a prerequisite for clinical decision making in patients with aortic regurgitation. Many methods have been proposed. Angiography is the accepted "golden" standard, but invasive, semiquantitative and based on assessment of contrast clearing from the left ventricle after aortic root injection during subsequent cardiac cycles[7]. However, the method is affected by many variables, including catheter position, amount of contrast injected, chamber size and function. The quantitative method is based on calculation of the regurgitation volume by subtracting the effective forward stroke volume (Fick method) from left ventricle total stroke volume. This method is limited by the problem of deriving left ventricular volume measurements from planar angiograms. This method is only valid in isolated valve regurgitation and in the absence of shunt lesions.

Doppler echocardiography is an attractive alternative non-invasive method, especially for serial evaluation of patients with aortic regurgitation. Current clinical color Doppler grading of aortic regurgitation is based on the measurement of the length of the regurgitant jet in the left ventricle and jet diameter or area in the parasternal short-axis view immediately under the aortic valve[1,3,5]. The grading of the severity of aortic regurgitation by scoring the jet length on a semiquantitative scale is largely dependent on systemic afterload and regurgitant orifice morphology and thus may overestimate the severity of aortic regurgitation[1,2]. Perry found in clinical studies that the jet diameter or area of the regurgitation jet relative to the size of the left ventricular outflow tract is more closely related to the severity of aortic regurgitation determined with angiography than the jet length method. According to his data, the cross-sectional jet area method showed the best correlation with angiography[1].

In our study we found a good correlation between angiography and the three color Doppler echocardiography methods for the quantification of aortic regurgitation severity. The jet length method may overestimate its severity as known from previous studies[1,2], but may also underestimate severity in certain conditions.

The jet diameter method seems to be a valid method for discrimination between mild and severe aortic regurgitation. A jet diameter-left ventricular outflow tract diameter ratio of 20% is used as cut-off value. Dolan et al.[3] found a cut-off value for the jet diameter ratio between 25% and 40% to discriminate between mild and severe aortic regurgitation. With reference to the studies of Dolan and associates[3], we could not distinguish the four individual grades of aortic regurgitation severity as described by Perry and colleagues[1].

Although there is a good correlation between the angiographic grading and jet area ratio method (Figure 1c), all the individual values were closely related. In clinical practice, discrimination between the different angiographic grades of aortic regurgitation is not possible. Furthermore, the jet area method is limited by technical difficulties. Planimetry is required and is subject to large measurement variability[6].

The time interval between cardiac catheterization and echocardiographic examinations is a limitation of our study. This may have resulted in a change of aortic regurgitation severity, that is influenced by the hemodynamic conditions of the patients. Also the aortic root angiographic examinations were not standardized and may be operator dependent.

Despite the limitations of angiography and color Doppler echocardiography for the assessment of aortic regurgitation, there is a good correlation between the two techniques. With reference to previous studies[1,3,4,5], we primarily use the jet diameter method for evaluating human tissue valve regurgitation during follow-up.

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Chapter 4

Reproducibility of color Doppler flow quantification of aortic regurgitation

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Abstract

Background. The preferred method for quantification of aortic regurgitation severity with color Doppler echocardiography is the assessment of the ratio of jet diameter to left ventricular outflow tract diameter and jet area to left ventricular outflow tract area. However, the reproducibility of these measurements is not known and may limit its clinical application. This study was performed to identify sources of variability and reproducibility of the echocardiographic data.

Methods. We examined 62 color Doppler echocardiographic examinations of patients showing isolated aortic regurgitation after human tissue valve implantation. The mean differences with standard deviations between paired measurements were calculated.

Results. The interobserver, intraobserver, and interframe variability showed a close agreement for the jet diameter and left ventricular outflow tract diameter measurements. The agreement for jet area and left ventricular outflow tract area measurements showed a small bias, but a large variance.

Conclusions. The reproducibility of jet-left ventricular outflow tract diameter is better than the jet-left ventricular outflow tract area measurement and is more accurate to assess the severity of aortic regurgitation from color Doppler images.

Introduction

Echocardiography allows the non-invasive evaluation of valve function during follow-up of patients with valvular regurgitation. Color Doppler echocardiography has proved to be sensitive and specific for the detection of valvular regurgitation, but its value for quantitative assessment of the severity of aortic regurgitation remains controversial[1-3]. The depth to which the regurgitation jet extends into the left ventricle allows a semiquantitative assessment, but has been shown to overestimate its severity in comparative studies with angiography[1,4]. Both the diameter or x-sectional area of the color Doppler regurgitant jet relative to the size of the left ventricular outflow tract were found to be better estimators of the severity[1,3]. However, these measurements require careful tracing and are subject to considerable variability. Therefore, the quantitative estimation of aortic regurgitation for color Doppler data in clinical practice may be limited by the reproducibility of the measurements[5].

Patients with a human tissue valve in the aortic position commonly have isolated aortic regurgitation and represent a suitable study group to assess the reproducibility of methods used for the quantification of aortic regurgitation color Doppler flow. Published studies have used correlation coefficients to measure the variability. This is a suboptimal method to compare the relative measurement error of different techniques[1,3,4,6-8].

The purpose of this study is to identify sources of variability and reproducibility of the Perry method, which is the most widely applied method for quantitative assessment of aortic regurgitation for color Doppler flow data[1].

Patients and methods

Study Patients

From January 1995 to July 1995, 80 patients underwent echocardiographic examination including color Doppler flow imaging as part of an ongoing follow-up study after implantation of an aortic allograft or autograft in the aortic position. Excluded from this study were 10 patients without aortic regurgitation, 3 patients with poor quality of echocardiographic study, 3 patients with aortic regurgitation only visualized in only one view, and 2 patients with multiple aortic regurgitant jets. The remaining 62 patients, 45 men and 17 women with a mean age 47 years (range, 20 to 87 years), were included in this study for assessment of reproducibility. In 35 patients the subcoronary implantation technique was used, and 27 patients had aortic root replacement. In 14 patients the aortic root was replaced with an aortic allograft and in 13 patients with a pulmonary autograft. The mean interval between operation and the echocardiographic studies was 2.8 years (range, 0.3 to 7 years).

All patients were in sinus rhythm with a heart rate below 100 beats/min and no patient had significant mitral valve disease or aortic stenosis on echocardiography.

Echocardiographic examination

To exclude intermachine differences, all examinations were performed on a Vingmed CFM 750 ultrasound system (Vingmed, Trondheim, Norway) using a 3.25 MHZ transducer.

During color Doppler examination the gain setting was standardized by starting at low gain and increasing until white noise appeared in the left ventricle cavity. The flow velocity was kept between 0.7 and 1.0 m/sec depending on the depth setting. The threshold of the flow velocity was set at 0.25 m/sec. Regurgitation flow signals were qualitatively described as laminar with an abnormal direction or as turbulent seen as a mosaic pattern.

During the examination, the imaging plane was angled to show the maximal regurgitant jet diameter or area. The maximal diameters and areas were measured on-line on the video screen from frozen images using a trackball. The mean values of measurements in two cardiac cycles were noted. All examinations were recorded on VHS video, without indication of which image was used for the measurements.

Echo analyses

The following measurements were made to assess the severity of aortic regurgitation according to Perry et al.[1] (Figure 1):

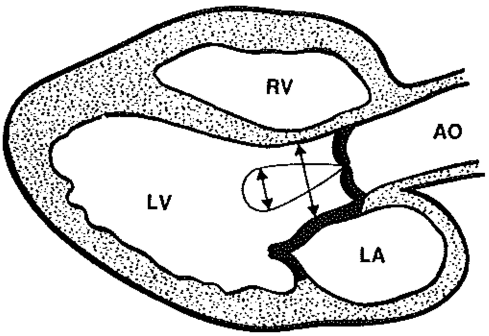
1. Left ventricular outflow tract (LVOT) diameter; the distance between the left side of the interventricular septum and anterior mitral valve leaflet in an end-diastolic parasternal long-axis view.
2. Regurgitant jet diameter; the maximal jet diameter just below the aortic valve in the parasternal long-axis view.
3. Left ventricular outflow tract area; the area just beneath the aortic valve in end-diastolic parasternal short-axis view.
4. Regurgitant jet area; the maximal area of the regurgitant jet just beneath the aortic valve in the parasternal short-axis view.

Measurement 1. Two experienced technicians (observer V and observer M) each measured 31 of the 62 color Doppler studies. The measurements were reviewed for the purpose of this study by one supervisor (observer T).

Measurement 2. The measurements were repeated at least 3 months later. Each observer, independently and blinded for previous measurements, selected two frames for each measurement after reviewing.

Reproducibility

Three types of variability were distinguished: (1) The interobserver variability indicating the differences between measurements of the three independent observers; (2) the intraobserver variability indicating the differences of the measurements by the same observer (for this purpose observer M and V each measured 16 of the original studies they analyzed); (3) the interframe variability indicating the difference between frames



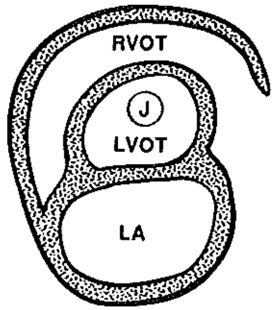


Figure 1. Left: Grading of aortic regurgitation by the maximal diameter of the color Doppler regurgitant jet relative to the left ventricular outflow (LVOT) diameter in the parasternal long axis view. *Right:* Grading of aortic regurgitation by the maximal area of the regurgitant jet relative to the LVOT area in the parasternal short axis view. LA, left atrium; LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; AO, aorta; J, jet.

obtained within one patient in a single examination. These measurements were performed by observers T and M.

Statistical Analysis

The reproducibility of all measurements was analyzed by calculating the mean differences ("bias") and the standard deviations (SD) ("variance") between paired measurements. A very reproducible measurement method has no bias and a low variance. Measurements may not be reproducible because of a systematic bias with possibly a low variance or because of a high variance with a low bias. Differences were plotted against their arithmetic mean and the limits of agreement were calculated (bias ± 2 SD), as described by Bland and Altman[8]. The significance of the mean difference between observers was tested with a paired t-test. Statistical significance was assumed when $p<0.05$. Quantitative data are reported as mean ± 1SD.

Table 1. Interobserver variablilty of the measurement to assess the severity of aortic regurgitation

	Obs. MV			Obs. VT			Obs. MT		
Measurements	Diff.	SD	p-value	Diff.	SD	p-value	Diff.	SD	p-value
LVOT diameter	0.10	0.31	0.01	0.00	0.15	ns	0.09	0.19	0.01
Jet diameter	0.03	0.14	ns	0.05	0.07	0.01	0.07	0.12	0.01
LVOT area	0.26	1.60	ns	0.04	0.67	ns	0.15	1.24	ns
Jet area	0.01	0.08	ns	0.03	0.09	ns	0.01	0.06	ns

Obs.; Observer; Diff.; difference, SD; standard deviation, LVOT; left ventricular outflow tract, ns; not significant

Table 2. Intraobserver variability of the measurements to assess the severity of aortic regurgitation

	Obs. M			Obs. V		
Measurements	Diff..	SD	p-value	Diff.	SD	p-value
LVOT diameter	0.08	0.20	ns	0.08	0.31	ns
Jet diameter	0.03	0.11	ns	0.06	0.11	0.04
LVOT area	0.22	1.58	ns	0.58	1.70	ns
Jet area	0.02	0.01	ns	0.03	0.12	ns

Obs.; Observer, Diff.; difference, SD; standard deviation, LVOT; left ventricular outflow tract, ns; not significant

Table 3. Interframe variability of the measurements to assess the severity of aortic regurgitation

	Obs. M			Obs. T		
Measurements	Diff.	SD	p-value	Diff..	SD	p-value
LVOT diameter	0.01	0.18	ns	0.02	0.11	ns
Jet diameter	0.02	0.16	ns	0.01	0.14	0.02
LVOT area	0.21	0.79	ns	0.02	0.46	ns
Jet area	0.01	0.09	ns	0.01	0.06	ns

Obs.; Observer, Diff.; difference, SD; standard deviation, LVOT; left ventricular outflow tract, ns; not significant

Results

The following ranges in the measurements for the assessment of the severity of aortic regurgitation were found: LVOT diameter 1.4 to 3.4 cm (mean 2.2 ± 0.5), jet diameter 0.05 to 1.2 cm (mean 0.3 ± 0.2), LVOT area 2.3 to 11.7 cm^2 (mean 5.3 ± 2.0) and jet area 0.06 to 1.0 cm^2 (mean 0.2 ± 0.2). There was no statistically significant difference in the on-line measurements of observers V and M ($p>0.05$).

Interobserver variability

The interobserver variability was evaluated by comparing paired measurements obtained by three different independent observers in separate reviewing sessions. The differences between the observers for the measurements with the standard deviation and p-values are shown in Table 1. There was a tendency for observer M to measure a slightly larger LVOT diameter and jet diameter than observer V and T. Observer T measured a smaller jet diameter. Other measurement differences can be explained by chance ($p>0.05$).

The agreement between the three observers for the measurements are shown in Figures 2a-d. The ratio of the length of the y-axis and the x-axis is 1:1 in all charts and allows visual inspection of the relative magnitude of the variability of the measurements. The agreement between observers was very close for the LVOT diameter and jet diameter measurements and was not influenced by the width of the LVOT or jet diameter. The agreement of LVOT area and jet area measurements showed a small bias but a large variance for the three observers and the reproducibility was less if compared with LVOT or jet diameter measurements. The variance of the differences for jet diameter, LVOT diameter, jet area, and LVOT area were within 25%, 13%, 30%, 45% of the mean value, respectively.

Intraobserver variability

The intraobserver variability was evaluated by comparing paired measurements obtained by the same observer in separate examinations from the same video tape. The differences between the same observer for the measurements with the standard deviation and the p-values are given in Table 2. For observer V there was a tendency to measure a larger jet diameter during the review session. The agreement between the same observers were similar to the agreement between different observers. There was a close agreement between LVOT diameter and jet diameter measurements. The LVOT area and jet area measurements showed a small bias but a large variance. The variance of the differences for the jet diameter, LVOT diameter, jet area, and LVOT area were 30%, 10%, 32% and 60% of the mean value, respectively.

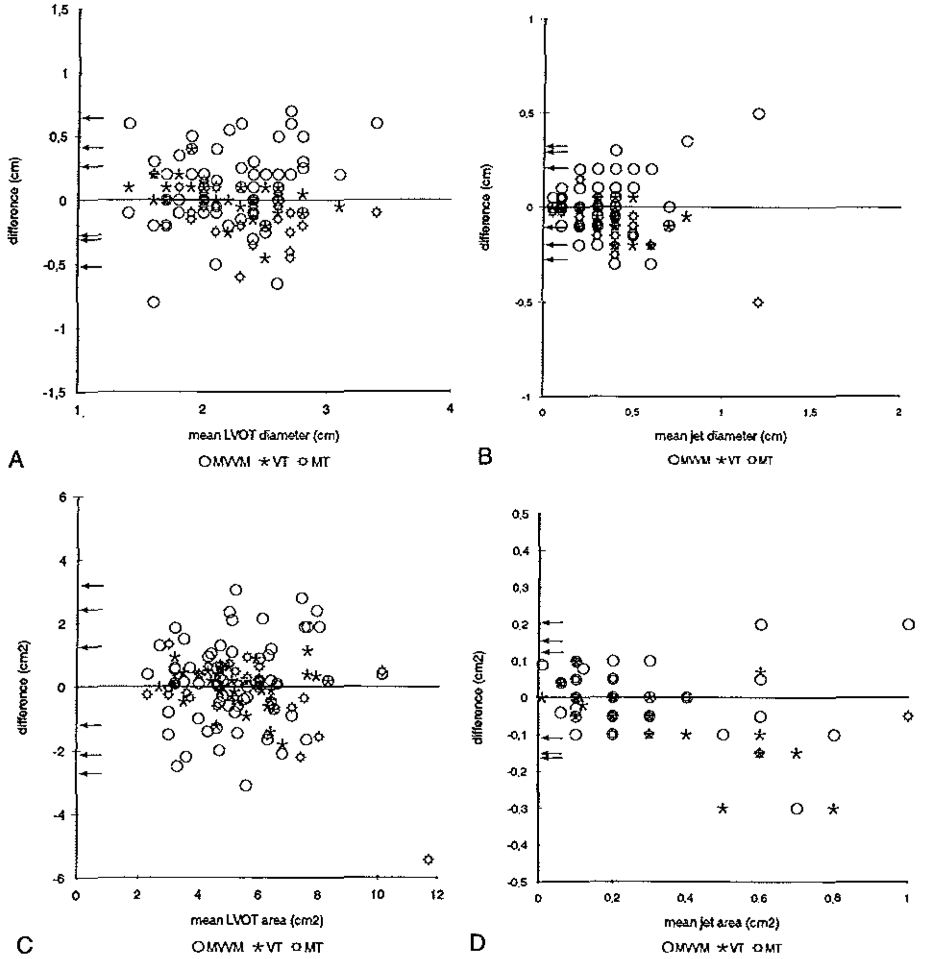


Figure 2. Agreement among three observers (MVVT,VT, and MT) for left ventricular outflow tract (LVOT) diameter (A), jet diameter (B), LVOT area (C) and jet area (D) measurement. Vertical axis represents the measurement differences between observers (bias), and the horizontal axis represents the arithmetic mean. Arrows point out the limits of agreement for each observer (bias ± 2 SD).

Interframe variability

The interframe variability was evaluated by comparing paired measurements made by the same observer during the same examination from two different frames. The results are shown in Table 3. Observer T showed only a statistical significant difference for the jet diameter measurement ($p=0.02$). The agreement between the two different frames for the same observer in the same examination was close for all measurements. The bias and variance was small for the diameter measurements as well as the area measurements.

Discussion

Different methods are used for the quantification of aortic regurgitation on color Doppler images and they all have their limitations[9]. In clinical practice, semiquantitative assessment is based on measurement of the length of the regurgitant jet in the left ventricle and jet diameter or area in the parasternal short-axis view immediately under the aortic valve[1,3,7]. The estimation of the severity of aortic regurgitation by scoring the jet length is largely dependent on systemic afterload and may overestimate the severity of aortic regurgitation. This has been demonstrated in vitro, whereby a jet diameter measured at its origin a better predictor was of regurgitant volume than jet length in different afterload condition[2]. This was further assessed in clinical studies[1]. Perry used angiographic grading as the gold standard for estimation of severity of aortic regurgitation. On echo he found that the jet diameter or area of the regurgitation jet relative to the size of the left ventricular outflow tract is more closely related to the severity of aortic regurgitation than jet length. On the basis of a good correlation with angiography, the echocardiographic x-sectional jet area method is now considered as the best technique.

The ratio of jet to LVOT diameter and jet area to LVOT area are the theoretically preferred method for semiquantitative estimation of aortic valve regurgitation. However, this method is subject to a large measurement variability. This variability is caused by the inaccuracies of tracing with a trackball and the selection of the still frame by the observers.

Previous studies concerned mainly the correlation rather than the reproducibility of the quantification method for the severity of aortic regurgitation[1,3,6,7]. These studies assessed the interobserver and intraobserver variability by calculating the correlation coefficient (r) between measurements. The interobserver and intraobserver correlations for the measurements in these studies are comparable with our results. In our study we found a interobserver and intraobserver correlation for LVOT-jet diameter and LVOT-jet area measurement of 0.82, 0.85, 0.74 and 0.92 respectively. These correlation coefficients may falsely lead to the conclusion that the reproducibility of the jet area method is sufficient.

The use of a correlation coefficient is however misleading[8,10]. A correlation coefficient measures the strength of a relation between two variables. The data of the two variables are plotted and a line of equality on which all points would lie if the variables gave the same data is drawn. This method gives insufficient information about the differences between two variables and may be influenced by outliers. Furthermore correlation coefficients do not compare the whole range of values between two variables. A high correlation can be caused by a very strong correlation between small values and at the same time a weak correlation between large values.

The clinical usefulness of a measurement technique depends on its ability to generate correct and reproducible measurements. The agreement as measured according to Bland and Altman is one of them[8,10].

The interobserver, intraobserver and interframe variability in our study showed a very close agreement for the LVOT diameter and jet diameter measurements (Figures 2a-b). The agreement for the LVOT area and jet area measurements showed a small bias but a large variance (Figure 2c-d). The interframe variability showed a close agreement for diameter measurements as well as area measurements. Thus, the reproducibility of jet diameter-LVOT ratio is better than the jet area-LVOT ratio measurement.

We therefore suggest that based on a high reproducibility of the measurement of the jet and LVOT diameter, these parameters should be preferred over the area measurements for the estimation of aortic regurgitation from color Doppler images. Despite the good correlation of area measurement method and angiography as found by Perry, the estimation of aortic regurgitation by color Doppler echocardiography in the follow-up of the individual patient should be based on the diameter measurements rather than area measurements.

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Results

Chapter 5

Aortic allograft implantation techniques: Pathomorphology and regurgitant jet patterns by Doppler echocardiographic studies

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Abstract

Background. The diagnosis of allograft-specific pathology by echocardiography has important consequences for patient counselling and research. This study describes the pathomorphologic findings and color Doppler jet patterns in a consecutive series of patients after allograft implantation with either the subcoronary implantation or root replacement technique.

Methods. From 1987 to July 1996, the subcoronary allograft implantation and root replacement technique were used in 82 and 70 patients, respectively. These patients comprised the study group.

Results. The incidence of paravalvular leaks and eccentric regurgitant jets was higher with the subcoronary implantation technique (41%) than with the root replacement (11%).

Conclusions. These findings support the concept of preservation of valve geometry after root replacement, as allograft-specific pathomorphologic abnormalities and eccentric jets are more common after subcoronary implantation of allografts. Learning effects, however, cannot be excluded as the cause of these abnormalities.

Introduction

Aortic valve replacement with an allograft is a well-established surgical treatment with good long-term results of cryopreserved[1-3] and homovital aortic donor valves[4].

Cross-sectional and color Doppler echocardiography have been used as non-invasive diagnostic tool to document aortic regurgitation and stenosis after allograft implantation[1-11]. However, there is a remarkable scarcity of systematic descriptive reports of pathomorphologic echocardiographic findings[5,12]. These data are important because echocardiography during follow-up is used for the dual purpose of patient counseling and research. In addition, detailed analysis of jet patterns on color Doppler echocardiography could reveal differences between implantation techniques.

The purpose of this study is to describe the pathomorphologic findings and regurgitant jet patterns on two-dimensional and color Doppler echocardiography in a consecutive series of adult patients with cryopreserved aortic allografts in whom either the subcoronary implantation or root replacement technique was used.

Patients and methods

Patients

Between 1987 and July 1996, 152 adult patients underwent implantation of a cryopreserved aortic allograft valve in aortic position at the Thoraxcenter Rotterdam. In 82 patients, the subcoronary implantation technique was used, and in 70 patients, aortic root replacement was performed. The mean age and the sex distribution of the patients were as follows: for subcoronary implantation 47.9 years (range, 21.8 to 83.6 years) and 70% male, and for aortic root replacement, 47.6 years (range, 17.3 to 75.7 years) and 63% male.

The subcoronary implantation technique was mainly used in patients with aortic valve pathology and intact aortic root. The pathologic process in this group was of rheumatic origin in 13 patients, a bicuspid valve in 25 patients, senile degeneration in 9 patients, and other in 4 patients. Thirty-one patients (38%) had operation for a pathologic condition attributed to infective endocarditis. Eleven of these 31 patients had active endocarditis at the time of implantation and 5 patients had an annular mycotic aneurysm. Initially, each sinus of Valsalva was excised (32 patients). Subsequently, the allograft valves were implanted with preservation of the aortic wall of the noncoronary sinus (50 patients)[13]. In recent years, the subcoronary implantation technique has been used less frequently.

The aortic root replacement technique was used in 49 patients with aortic valve disease associated with major aortic root pathology, which was caused by acute, infective endocarditis in 4 patients. Root replacement was also preferred in 21 patients with aortic valve disease that was not associated with aortic root pathology. The valvular pathologic process in these patients was of rheumatic origin in 2, a bicuspid valve in 5, senile degeneration in 3, and infective endocarditis in 11. Aortic root replacement was performed with a free-standing root with a variable length of donor aorta.

The aortic allograft valves were cryopreserved and supplied mainly by the Heart Valve Bank Rotterdam, through Bio Implant Services, Leiden, The Netherlands. The mean internal diameter of the allografts was 23.4 mm (range, 19 to 28 mm).

The hospital mortality rate after subcoronary implantation and aortic root replacement was 4.8% (4 patients) and 4.2% (3 patients), respectively. The cause of death were cardiac failure unrelated to allograft valve failure. The overall survival rate by Kaplan-Meier analysis at 5 years was 81% (n=8, 95% CL 72% to 89%) after subcoronary implantation and 94% (n=4; 95% CL 92% to 97%) after aortic root replacement. The 5-year freedom from reoperation for allograft failure after subcoronary implantation and aortic root replacement was 86% (n=10, 95% CL 82% to 90%) and 93% (n=2, 95% CL 88 to 98%). These differences, evaluated with the log-rank test, were not significant ($p>0.05$).

The median duration of follow-up for the hospital survivors was 4.2 years (range, 1 month to 7.7 years) after subcoronary implantation and 2.1 years (range, 1 month to 6.3 years) after aortic root replacement.

Echocardiographic methods

Between 1987 and 1993, the morphology and function of the aortic allograft valve was assessed by serial precordial echocardiography. The peak velocity across the aortic allograft valve was measured with continuous-wave Doppler in the apical view.

The pattern of the regurgitant jet was reviewed in the parasternal long-axis and short-axis, and in the four-chamber apical view. Aortic regurgitation was assessed by the jet length method on a scale of 0 to 4, and the data from patients with grade 2 aortic regurgitation or higher were used to describe the jet patterns after allograft implantation. These regurgitation jets extended into the left ventricular outflow tract sufficiently to allow analysis.

The echocardiographic examinations were performed on a Vingmed CFM 750 ultrasound system (Vingmed, Trondheim, Norway). The flow velocity was set between 0.7 and 1.0 m/s, depending on the depth. The threshold of the flow velocity was always set at 0.25 m/s.

Echocardiographic follow-up

For the analysis of the pathomorphology, echocardiograms scored by the jet length method were available in 79 patients who underwent a subcoronary implantation with a median interval after operation of 3.5 years (range, 2 months to 6.8 years). In the group having aortic root replacement, an echocardiogram was available for 57 patients with a median follow-up interval of 1.8 years (range, 4 months to 5.3 years). Unavailable for echocardiographic analysis were 6 patients who died in hospital, 3 patients who were lost to follow-up, and 2 patients with an incomplete echocardiographic examination. For 5 patients who had operation recently, no echocardiogram was available.

Statistical analysis

Survival and freedom from reoperation for allograft failure were analyzed according to the Kaplan-Meier method[14]. The differences between curves were evaluated with the log-rank test. The unpaired *t*-test was used to look for differences in peak velocity across the valves. A p value of less than 0.05 was considered significant.

Results

Allograft stenosis

For the entire group of patients, the mean value of the peak velocity across the aortic allograft valve after subcoronary implantation was 1.8 m/s (range, 1.1 to 6 m/s) and after root replacement 1.4 m/s (range, 1.0 to 2.1 m/s). This difference was not significant ($p>0.5$). The reported peak velocity across the normally functioning native aortic valve is 1.3 m/s (range, 1.0 to 1.7 m/s)[15].

After subcoronary implantation, 4 patients (5%) had a pathologic gradient across the valve. One patient had reoperation for aortic stenosis 3.6 years after allograft implantation. On visual inspection, the explanted allograft valve showed severe calcified deposits on the leaflets. Another patient has moderate aortic stenosis (peak velocity of 2.6 m/s) and is in New York Heart Association class I after 5.6 years of follow-up. Combined aortic stenosis and regurgitation was observed in 2 patients. The valve stenosis was caused by inward displacement of the allograft annulus resulting from dehiscence at the suture line with paravalvular regurgitation.

After root replacement, no pathologic gradients were encountered.

Paravalvular leakage and pseudoaneurysm

Paravalvular leakage was defined as a perfused space between the native aortic wall and the allograft. Typically, the onset of turbulent flow on color Doppler occurred during diastole between the proximal and distal suture lines (Figure 1).

During echocardiographic follow-up, one or more paravalvular leaks were detected in 15% (12/79) of patients who had subcoronary implantation. Four of these patients had reoperation for severe paravalvular leakage. Two patients of them, who had combined aortic stenosis and regurgitation have been mentioned already. In the 2 others, the paravalvular leak was caused by dehiscence of sutures, but no stenosis was observed. One patient with a small paravalvular leak had a subannular mycotic aneurysm, which caused systolic compression of the left coronary artery. This patient required reoperation for intermittent ischaemia. In the remaining 7 patients, the paravalvular leakage was not of haemodynamic importance, and no progression in severity has been observed during a mean follow-up of 5.2 years (range, 3.8 to 7.4 years).

Pseudoaneurysm was defined as an echo-free space between the aortic allograft and native aortic wall and was encountered in 4 patients (3%) in the study. Pseudoaneurysms are due to partial dehiscence at the proximal or distal suture line. A pseudoaneurysm at the proximal anastomosis after root replacement was detected in 2 patients with Marfan disease (Figure 2). On color Doppler echocardiography, there was late diastolic turbulent flow. Both patients underwent reoperation. In 2 patients with subcoronary implantation, a supraannular pseudoaneurysm was detected at the distal suture line. On color Doppler echocardiography, diastolic flow was detected between the allograft wall and native wall, but no continuity of this turbulence into the left ventricular outflow tract was seen. One of these patients had reoperation for aortic regurgitation, and dehiscence of the distal suture line was confirmed on visual inspection. The other patient is in New York Heart Association class I at 2.2 years of follow-up.

Jet Pattern

To investigate the influence of the allograft implantation technique on jet morphology, transvalvular aortic regurgitation jets were examined according to their jet pattern. These jets were found in 30 (38%) of 79 available echocardiograms after subcoronary implantation and in 3 (5%) of 57 available echocardiograms after aortic root replacement.

In the subcoronary implantation group, a central jet origin was found in 24 valves (80%) and a commissural origin in 6 valves (20%). Of the 30 regurgitant jets, 12 (40%) had a noneccentric trajectory and were directed centrally into the left ventricular outflow tract. An eccentric jet pattern was observed in 18 patients (60%). Fourteen jets were directed to the ventricular surface of the anterior mitral valve leaflet and 4, to the interventricular septum. In patients with subcoronary implantation, no relation was found between jet direction and resection or preservation of the noncoronary sinus.

In the 3 patients who had aortic root replacement, the regurgitant jets originated centrally from the aortic valve. One jet had an eccentric trajectory and was directed to the anterior mitral valve leaflet. The other 2 jets had a central trajectory in the left ventricular outflow tract.

During the analysis, two possible confounding factors for semiquantitative assessment of aortic regurgitation in allografts were identified. First, 11 of the 24 jets with a central origin were directed towards a commissure, and on the parasternal short-axis view, the regurgitant jet was oval. These jets started with an intravalvular trajectory before they hit the left ventricular outflow wall and projected into the left ventricular outflow tract. Second, multiple regurgitant jets were seen in 7% (10/136) of the patients.

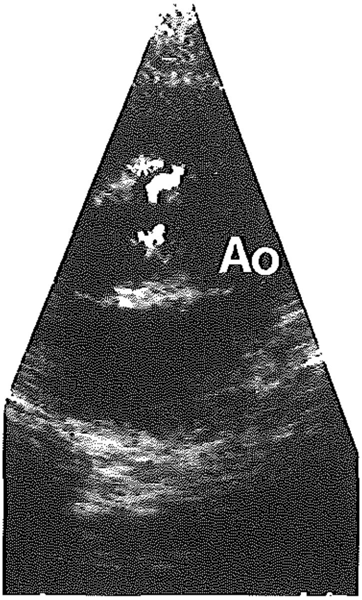

Figure 1

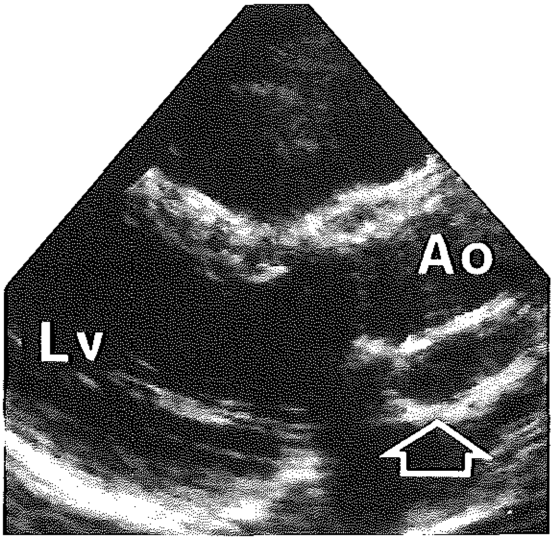

Figure 2

Figure 1. Postoperative color Doppler echocardiogram in the parasternal long-axis view after a subcoronary implantation of allograft aortic valve. The asterisk indicates the paravalvular leak. Turbulent flow was detected during diastole between the native aortic wall and the allograft. A small centrally orginating regurgitant jet is also present. (Ao; aorta).

Figure 2. Postoperative epicardial two-dimensional echocardiogram in the parasternal long-axis view after allograft root replacement. The arrow points at a pseudoaneurysm located at the proximal anastomosis. (Ao; aorta, Lv; left ventricle).

Discussion

Two-dimensional and color Doppler echocardiography are essential, noninvasive tools for the follow-up of patients with an aortic allograft. Serial postoperative examinations should detect early and late allograft failure because subcoronary implantation is prone to technical error and the long-term durability of allografts is limited[1-5,7-10,16]. Proper interpretation is essential for the decision whether to reoperate. Echocardiography has a great potential as a research tool to answer many relevant questions, such as the preferred implantation technique and the influence of donor-recipient interactions and allograft preservation methods on valve degeneration[10,11,17]. For this purpose, routine echocardiographic follow-up examinations may not be sufficient[10]. For patient counseling and research, allograft-specific pathology on cross-sectional and color Doppler echocardiography should be recognized but has drawn limited attention to date.

This study confirms previous echocardiographic observations on the favorable low transvalvular gradients of aortic allografts after subcoronary implantation and root replacement[3,5-7,9]. In our experience, there is a significantly higher incidence of reoperation for aortic regurgitation and stenosis after subcoronary implantation than after root replacement.

Oechslin and colleagues[12] studied the pathomorphologic findings with the current echocardiographic techniques after allograft aortic valve implantation. They described pseudoaneurysms in 73% (22/30) of the patients after subcoronary implantation and root replacement. Root replacement was performed as an inclusion cylinder and, in some patients, as a freestanding root. No cases of paravalvular leakage were reported. In contrast, we detected a pseudoaneurysm at the proximal or distal anastomosis in 3% of all allograft patients. In the patients with root replacement and Marfan's disease, we did not await further progression and performed a reoperation, although the aortic valve was competent. One patient with a pseudoaneurysm at the distal suture line after subcoronary implantation required reoperation for aortic regurgitation. As expected, paravalvular leaks occurred only after subcoronary implantation in 15 % of our patients, but reoperation for aortic valve regurgitation or mixed valve disease was required in 5%. In only one patient were the sequelae of acute infective endocarditis not completely abolished by subcoronary allograft implantation, and a residual subannular, mycotic aneurysm persisted. The difference in the incidence of echo-free spaces around allografts on echocardiography in the study of Oechlins and associates[12] and our study (73% versus 13%) can only in part be explained by different implantation techniques.

In this study, the morphology of jet patterns on color Doppler echocardiography was analyzed to detect differences between the subcoronary implantation technique with resection of all three sinuses of Valsalva compared with the technique of Ross[13], in which the non-coronary sinus is preserved. There were no differences in incidence or jet direction between the two techniques. We assume that jets originating centrally and projecting centrally into the left ventricular outflow tract are the result of a suboptimal match between host annulus and donor size. The most striking observation was the difference in incidence of eccentric jets between subcoronary implantation and root replacement. This finding supports the concept that the advantage of root replacement is better preservation of the geometry of the donor leaflets with less turbulent flow during closure. However, the learning curve might have influenced these results. It is unclear whether this finding has consequences for late valvular function.

The relevance of eccentric jets for the quantification of aortic regurgitation has been noticed previously by Jaffa[5]. They found a 30% incidence of sharply angulating jets in allografts. In our study, there was a particularly high incidence of centrally originating jets, with an initial eccentric trajectory at the level of the leaflets, that hit the left ventricular outflow wall and thereafter projecting into the left ventricle. This occurred more commonly in subcoronary implanted allografts (11/24 or 46%). In addition, with multiple jets, an eccentric jet pattern may have confounding consequences for the quantification of aortic regurgitation after subcoronary implantation. These factors require more than routine attention during assessment of echocardiograms for the purpose of research.

We conclude that allograft-specific pathology on echocardiography, such as pseudoaneurysm or paravalvular leaks and eccentric jets are more common after subcoronary implantation of allografts. Analysis of jet patterns with color Doppler echocardiography supports the validity of the concept of preservation of the geometry of the aortic root after root replacement. Quantification of regurgitant jets may frequently be confounded by eccentricity and multiple jets.

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Chapter 6

Subcoronary implantation or aortic root replacement for human tissue valves: Sufficient data to prefer either technique?

Ann Thorac Surg 1995;60:S83-86

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Abstract

Background. The aortic root replacement technique with aortic allograft or pulmonary autograft might be superior to the subcoronary allograft implantation technique with regard to aortic regurgitation. We explored the influence of the learning process on the incidence of reoperation and the severity of postoperative aortic regurgitation assessed by color Doppler echocardiography.

Methods. The subcoronary implantation technique was used in 81 patients, and root replacement was done in 63 patients. The first 30 patients of each group were considered as the surgeons' learning curve.

Results. Reoperations were more common in the subcoronary implantation group. After exclusion of early reoperations, the median regurgitation score based on echocardiographic examination was 0.22 in the first 30 patients from the subcoronary implantation group and 0.14 in the root replacement group. The subsequent operated patients from these groups had regurgitation scores of 0.20 and 0.17, respectively. Statistical analysis of these data showed no significant difference.

Conclusions. This interim report suggests that the learning curve for the surgical procedure and the grouping of echocardiographic data influence the interpretation of follow-up studies. The superiority of either technique with regard to aortic regurgitation has yet to be proved.

Introduction

Human tissue valves are increasingly used for aortic valve replacement and good long-term results have been reported[1,2]. It is still under debate, however, which surgical technique to use: the subcoronary implantation or aortic root replacement?

The disadvantage of root replacement is the radical surgical approach for aortic valve replacement. An argument in favor of the implantation of the human tissue valve as a functional unit is the lower incidence of early reoperation compared with the subcoronary implantation technique[3-5]. Furthermore, recent reports have suggested that aortic regurgitation on color Doppler echocardiography is less prominent after aortic root replacement then after subcoronary implantation[3,4].

Several factors may influence the results of either technique, and the learning curve for the surgical procedure is an important one. Other factors, such as the grouping of echocardiographic data, also may have influenced the interpretation of previous follow-up studies[6,7]. The purpose of this interim report is to explore the influence of the learning process on the incidence of reoperation and the severity of postoperative aortic regurgitation as assessed by color Doppler echocardiography.

Patients and methods

Patient population

From May 1987 till June 1994, 144 adult patients underwent implantation of a human tissue valve in the aortic position. In 81 patients the subcoronary implantation technique was used, and in 63 patients the aortic root replacement technique was done. An aortic allograft was used in all subcoronary implantations and in 37 of the root replacements. The pulmonary autograft was used for aortic root replacement in 26 patients. The mean age and sex distributions of the patients undergoing the different procedures were as follows: subcoronary implantation, 47 years (range, 17 to 83 years) and 31% female; allograft root replacement, 44 years (range, 17 to 74 years) and 41% female; autograft root replacement, 26 years (range, 17 to 42 years) and 50% female.

The hospital mortality rates for subcoronary implantation and aortic root replacement patients were 4.9% (4 patients) and 4.8% (3 patients), respectively. The median duration of follow-up for the hospital survivors was 28 months (range, 2 to 81 months) in the subcoronary implantation group and 22 months (range, 2 to 62 months) in the aortic root replacement group.

Surgical techniques

Surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St. Thomas solution) and topical cooling.

The subcoronary implantation technique was initially applied with scalloping of each sinus of Valsalva in 32 patients. Subsequently, the valves have been implanted in 49 patients with preservation of the aortic wall of the noncoronary sinus, a technique introduced by Ross[8]. Aortic root replacement with the aortic allograft or pulmonary autograft was performed with reimplantation of the coronary ostia[9]. In cases in which the autologous pulmonary valve was used, it was replaced by a pulmonary allograft[10,11].

There were important differences in the indication for a particular procedure. The allograft root replacement technique was mainly used in patients with major aortic root pathologic process or valve disease associated with aneurysm of the ascending aorta. The autograft root replacement and the subcoronary implantation technique were mainly performed in patients with isolated aortic valve disease. The autograft root replacement technique was chiefly applied in young adult patients.

Echocardiographic methods

Since March 1993 the structure, function, and competence of the implanted allograft valves in these patients have been assessed by echocardiography at 6- to 12- month intervals. The protocol for precordial echocardiographic examinations of allograft and autograft recipients includes the following. All examinations are performed on a Vingmed CFM 750 ultrasound system (Vingmed, Trondheim, Norway) with a 3.25 MHz transducer. Two technicians were trained and instructed to perform the echocardiography. The gain is standardized during color Doppler examination of the left ventricular outflow tract for regurgitant flow signals by starting at low gain and adjusting the gain upward until white noise just appears. The flow velocity reject is set at 0.25 m/s. The instrument settings at the first examination of the patient are noted and used during follow-up examinations. Aortic regurgitation is considered to be present by color Doppler examination when diastolic flow signals originating from the aortic valve are visualized in the left ventricle outflow tract. This flow is described qualitatively described as laminar flow with an abnormal direction (away from the aortic valve during diastole) or as turbulent flow seen as a mosaic pattern.

The severity of aortic regurgitation is determined according to Perry and associates[11]. The ratio of the regurgitant jet diameter to the systolic left ventricular outflow tract diameter is measured in the parasternal long-axis view. This ratio will be referred to as the jet diameter ratio. During the examination, the imaging plane is angled to demonstrate the maximal diameter of the regurgitant jet. The jet diameter is measured just below the aortic valve. Diameters are measured on-line on the video screen by planimetry using a trackball to trace the frozen images. The mean values of measurements in two cardiac cycles are noted. The results are reviewed by one cardiologist. These measurements correlate well with the angiographic estimates of the severity of aortic regurgitation. A numeric grade was assigned according to the available threshold values, as determined by Perry and colleagues[11]: grade 0, jet diameter ratio 0;

grade 1, ratio 0.01 to 0.24; grade 2, ratio 0.25 to 0.46; grade 3, ratio 0.47 to 0.64; grade 4, ratio 0.65 or greater.

Echocardiographic follow-up

Postoperative echocardiograms were available in 50 patients who underwent subcoronary implantation, with a median interval after operation of 32 months (range, 12 to 78 months). In 39 patients with aortic root replacement, an echocardiogram was available with a median postoperative interval of 23 months (range, 6 to 62 months). Unavailable for echocardiographic analysis were 7 patients who died in hospital. Also excluded were the 37 patients who were within the 6-month postoperative follow-up and 9 patients who had reoperations. Two patients were lost for echocardiographic follow-up.

Data analysis

Kaplan-Meier curves were constructed to estimate the 2-years cumulative incidence of reoperation. Differences between curves were evaluated with the log-rank test.

Box plots were used to depict the distribution of the jet diameter ratios[12]. The box shows the median and the 25% to 75% the interquartile range, and contains 50% of the measured jet diameter ratios. Moreover, the box plots show the values within 1.5 times the interquartile range and outlying values.

The numerical grade for severity of aortic regurgitation and the median regurgitation scores were compared with a nonparametric test (Mann-Whitney)[13].

Results

Assessment of the severity of postoperative aortic regurgitation allows us to describe which surgical technique - the subcoronary implantation or aortic root replacement - is the technique of choice. This was analyzed by the incidence of reoperation and by the severity of aortic regurgitation during echocardiographic follow-up.

Successful implantation of human tissue valves is highly related to the surgeon's experience with the technique of subcoronary implantation and root replacement technique. Therefore, we considered the results from the first 30 operated patients of each group as the learning curve. The incidences of reoperation in the first 30 operated patient and in the subsequent operated patients were compared for both techniques.

The echocardiographic analysis was used to detect functional postoperative differences between the implantation techniques. Therefore, reoperations were excluded in this echocardiographic analysis. To assess whether the echocardiographic data were still influenced by the learning curve, we compared the data of the first 30 patients with the data of the subsequent operated patients.

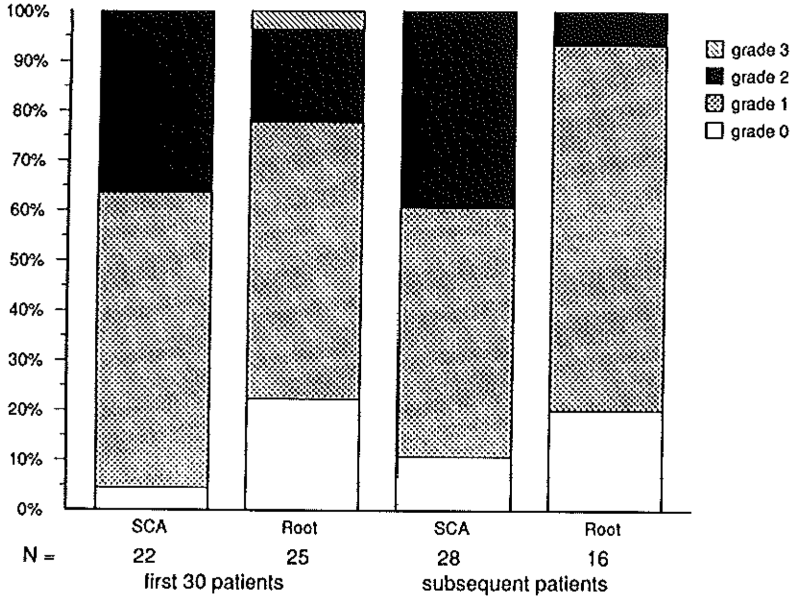

Figure 1. Cumulative distribution of severity of aortic regurgitation after grading of jet diameter ratios in the first 30 operated and subsequent operated patients for both implantation techniques. (SCA; subcoronary implantation).

Reoperation

The total 2-years cumulative incidence of reoperation was 11% (six of 81) in the subcoronary implantation group and 7% (three of 63) in the aortic root replacement group. One patient was excluded from further analysis because the indication for reoperation was not considered to contribute to the description of the learning curve. This patient received a pulmonary autograft and had reoperation for severe aortic regurgitation due to recurrent acute rheumatic fever[14]. Reoperation for severe aortic regurgitation could be considered as an expression of the learning curve in 8 of 144 patients (2-year rate 8%). In two patients who had reoperation in the subcoronary implantation group, the learning errors were identified as errors in judgement, and root replacement would have been indicated. Four patients with subcoronary implantation and two patients with an allograft root replacement had reoperations because of technical errors.

Five reoperations occurred among the first 30 patients from the subcoronary implantation group (2-year rate 17%). There was one reoperation in the subsequent 51 patients from the subcoronary implantation group (2%). In the first 30 patients from the root replacement group, there were two reoperations (2-year rate 7%). The subsequent

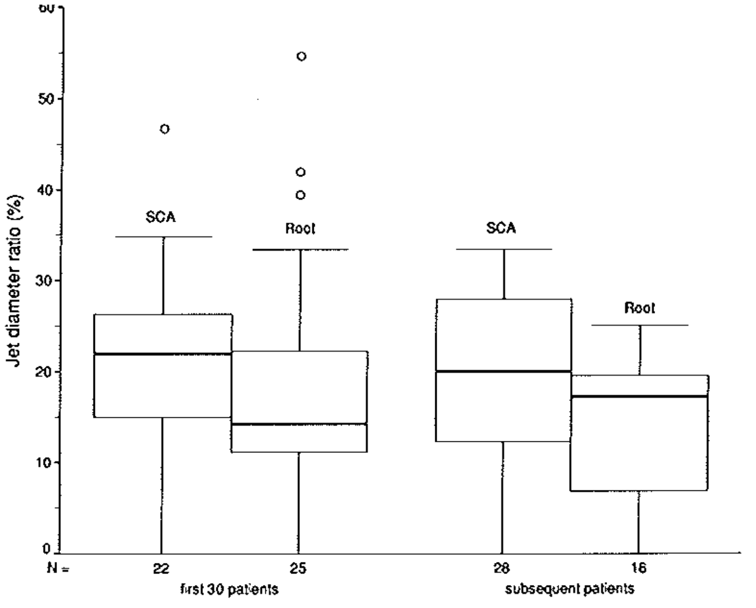

Figure 2. Median jet diameter ratios for the first 30 and subsequent operated patient groups for the subcoronary implantation (SCA) and root replacement techniques. Median value is denoted (heavy line). The interquartile range is included within the box, which contains 50% of the measured jet diameter ratios. The values within 1.5 times the interquartile range are included (error bar). The outlying values are denoted (circles).

33 patients with root replacement were free of reoperation. These differences in the cumulative incidence of reoperation were not statistically significant (p>0.20).

Echo Doppler analysis

The jet diameter ratio was used to estimate the severity of the aortic regurgitation.
The numeric grades for the severity of aortic regurgitation are shown in Figure 1. Eight and five patients among the first 30 patients from the subcoronary implantation and root replacement groups, respectively, had a regurgitation grade of 2 or more. The subsequent patients from both groups had a significant difference in the severity of aortic regurgitation: 11 subcoronary implantation patients had grade 2 or more aortic regurgitation, in contrast to only 1 patient who had a root replacement (p=0.02).

When median jet diameter ratios were compared, different results were found (Figure 2). The median jet diameter ratio was 0.22 (range, 0 to 0.46) in the first 30 patients with a subcoronary implantation and 0.14 (range, 0 to 0.54) in the first 30 patients with a root replacement.The subsequent patients from the subcoronary implantation and root replacement groups had median jet diameter ratios of 0.20 (range, 0 to 0.30) and 0.17 (range, 0 to 0.25), respectively. These differences in median jet diameter ratios were not statistically significant (p >0.05). If the total experience for both

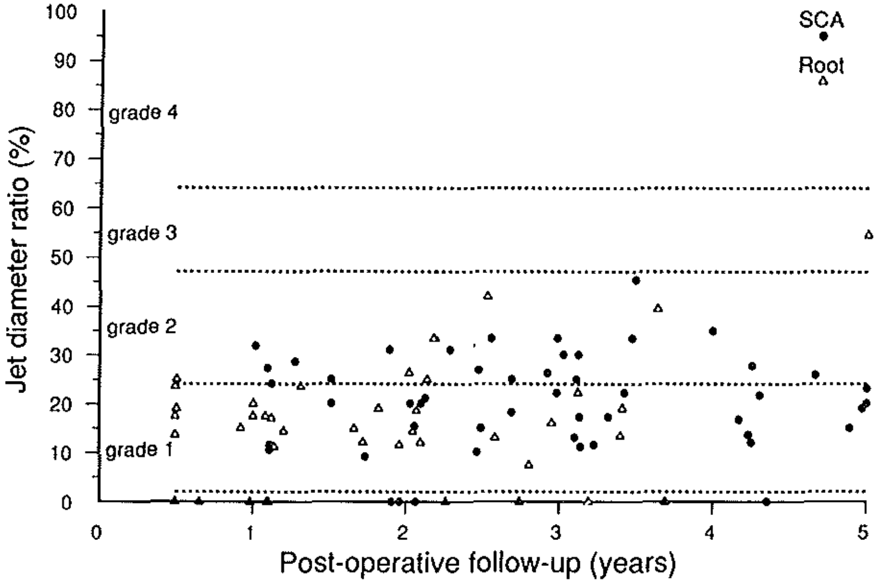

Figure 3. Distribution of jet diameter ratios during postoperative follow-up. (Dashed lines; thresholds determined by Perry and colleagues[11]; SCA; subcoronary implantation).

techniques was analyzed, the median jet diameter ratios were 0.21 (range, 0 to 0.46) in the subcoronary implantation group and 0.15 (range, 0 to 0.54) in the root replacement group. This difference was statistically significant (p=0.02).

Discussion

Replacement of the aortic valve as a total root might be superior to allograft implantation with the subcoronary allograft implantation technique with regard to aortic valve regurgitation.

There are technical advantages in the aortic root replacement technique. The matching of allograft size with the host annulus is less critical, and the implantation of the graft as functional unit is less prone to surgical error[4]. In general, root replacement is a firmly established surgical technique as shown by the use of other types of valved conduits. A disadvantage of root replacement is its radical approach as a technique for aortic valve replacement. During late follow-up, calcification of the original allograft aortic wall is common. This may have consequences for the development of aortic valve regurgitation and may eventually influence the complexity of reoperations[15]. Aortic root replacement may be the preferable technique, but firm data to support this contention are not available. Because long-term clinical results concerning these problems are yet to come, the choice is currently based on the incidence of early reoperation and the development of aortic regurgitation on color Doppler echocardiography.

Reoperations were more common in the first 30 patients after subcoronary implantation than after root replacement. This finding after subcoronary implantation is comparable to the early experience of Jones[3], who reported five reoperations in the first 31 patients. The incidence of early reoperation suggests that surgical experience is an important factor and a learning curve is apparent. In clinics with a resident training program, this is an additional argument for performing the root replacement technique. For surgeons with experience in the subcoronary implantation technique, the choice is more complex and largely supported by echocardiographic follow-up data.

Recent echocardiographic studies have shown a lower incidence of aortic regurgitation after root replacement than after subcoronary implantation of human tissue valves[3,6]. In these studies, the consequences of the surgeons' learning curve were included in the echocardiographic analysis. Thus, the results may be biased by a learning effect, which is more prominent in the subcoronary implantation technique[3,6]. We excluded from our echocardiographic data early reoperations for aortic regurgitation due to plain technical failure. After this adjustment, we observed no major differences between the root replacement and the subcoronary implantation technique.

If our same data are grouped by grading of the severity of regurgitation according to Perry and associates[11], less aortic regurgitation was observed with the root replacement technique than with the subcoronary implantation technique. This contradiction is explained by the following considerations. Grading of aortic regurgitation with color Doppler echocardiography for the purpose of this analysis lacks sufficient validation. The thresholds as defined by Perry and colleagues[11] were based on a limited number of observations in patients with grades 1 and 2 regurgitation. Basically, these measurements differentiate between grade 1 or 2 (minor) and grade 3 or 4 (major) aortic valve regurgitation. Figure 3 shows that the jet diameter ratios are clustered around the threshold value between grade 1 and 2. A small shift of this threshold value has major consequences for the interpretation of echocardiographic data and study results. In addition, from a statistical point of view, the original jet diameter ratios are preferred over grouping of data. Grading is useful in clinical practice but is less valid for calculated comparisons of implantation techniques.

On the basis of our echocardiographic analysis, it appears that aortic root replacement is not superior over the subcoronary implantation technique. The higher incidence of reoperation during the learning curve of the subcoronary implantation technique is an important limitation. Longer clinical follow-up with a predetermined echocardiographic protocol could provide more definite information on both implantation techniques with regard to long-term aortic valve function.

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Chapter 7

Human tissue valves in aortic position; determinants of reoperation and valve regurgitation

Submitted

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Abstract

Background. Human tissue valves are increasingly used for aortic valve replacement, but they have a limited durability, that is influenced by several interrelated determinants. Analysis of these determinants in relation to valve regurgitation as measured by serial echocardiography, can be done by using hierarchical linear modeling.

Methods. Data from 204 patients that received a human tissue valve in aortic position was analyzed. 154 cryopreserved aortic allografts were implanted in 152 patients, 83 by means of subcoronary implantation and 71 with the root replacement technique. 52 patients had root replacement with a pulmonary autograft. Mean follow-up was 2.2 years (range, 0.5 to 7.2 years). Color Doppler echocardiography was employed to repeatedly measure the severity of aortic regurgitation by using the jet length and jet diameter method (ratio of jet diameter and LVOT diameter). Multi-level hierarchical linear models were used to estimate for each individual patient initial aortic regurgitation (intercept), its change over time (slope), and the effect of several potential determinants of durability on aortic regurgitation.

Results. Mean initial aortic regurgitation was 1.11 grade using the jet length method, with an increase of 0.09 grade per year. Using the jet diameter method, initial aortic regurgitation was 0.15 grade with an annual increase of 0.09 grade. Valves implanted with the subcoronary implantation technique had more initial aortic regurgitation compared to those implanted with the root replacement technique. The difference in initial aortic regurgitation persisted even after elimination of the surgical learning phase for the subcoronary implantation technique. Progression of aortic regurgitation over time was not different for either technique.

Conclusions. With regard to initial aortic regurgitation, aortic root replacement is superior to the subcoronary implantation technique. Progression of aortic regurgitation over time is small, and no determinant of durability has an important influence at medium term follow-up.

Introduction

Aortic allograft and autografts are increasingly used for aortic valve replacement and good long-term results have been reported[1-12]. Early and late valve function is determined by several interrelated determinants including patient characteristics, the type of valve used and most important whether subcoronary implantation or aortic root replacement is used.

The need for reoperation has been used to assess the results of either surgical technique, but represents a rather crude endpoint. Serial echocardiographic examinations could offer a non-invasive means to monitor the process of valve degeneration by assessment of aortic regurgitation. However, no late echocardiographic follow-up data are available that take into account the above mentioned determinants of durability[13]. This prospective, serial color Doppler echocardiographic study was conducted to assess the degree of aortic regurgitation after allograft or autograft implantation and its change over time.

Patients and methods

Patients

From 1987 to July 1996, 206 human tissue valves (154 cryopreserved aortic allografts and 52 autografts) were implanted in the aortic position in 204 adult patients. Eighty-three allografts were implanted in the subcoronary position in 82 patients and 71 allografts were used for aortic root replacement in 70 patients. The pulmonary autograft was used for aortic root replacement in 52 patients.

The mean age and sex distributions of the patients were as follows; subcoronary implantation 48 years (range, 22 to 84 years) and 70% male, aortic root replacement with an allograft 48 years (range, 17 to 76 years) and 63% male, and aortic root replacement with pulmonary autograft 30 years (range, 16 to 52 years) and 64% male. The left ventricular function was assessed semi-quantitatively by cineangiography or echocardiography and was categorized as good (n=123), moderate or severely impaired (n=45). The data were incomplete in 38 patients.

Previous surgery on the aortic valve and/or left ventricular outflow tract was performed in four (4.8%) subcoronary implantations, in 17 (23.9%) allograft root replacements and in 16 (30.1%) pulmonary autograft root replacements.

The patients were operated at the University Hospital Rotterdam - Dijkzigt. The subcoronary implantation technique was mainly used in patients with isolated valve pathology. A severely disturbed aortic root anatomy was found in 12 patients (5.8%). Annular destruction and/or burrowing abcesses due to infective endocarditis was diagnosed in seven patients (8.4%). Annulo-ectasia with proximal root dilatation was found in three patients and two patients had a dilatation of the ascending aorta with an asymmetric dilatated sinus of Valsalva.

In 32 subcoronary implantation procedures each sinus of Valsalva was scalloped. In recent years, 51 allograft valves were implanted with preservation of the aortic wall of the non-coronary sinus as described by Ross[14].

The aortic root replacement with aortic allograft or autograft was performed as a free-standing root with a variable length of donor aorta. Initially, root replacement with an aortic allograft was performed in aortic valve disease associated with major root pathology. This occured in 49 patients. Annulo-aortic ectasia with proximal root dilatation, asymmetric dilatation of the sinus of Valsalva or fusiform dilatation of the ascending aorta excisted in 31 patients (43.7%). Eleven patients had an acute aortic dissection in the setting of Marfan disease, a bicuspid aortic valve or an intimal tear into the coronary ostium. Two patients had chronic dissection and one patient had a "porcelain" aortic root. Four patients had an annular destruction and/or burrowing abcesses due to infective endocarditis.

Pulmonary autograft root replacement was mainly used in young adult patients with isolated valve pathology. The pulmonary root was replaced by a pulmonary allograft. In 9 of the 52 autograft root replacement operations, the aortic root anatomy was disturbed by annulo-ectasia with proximal root dilatation or by fusiform dilation of the ascending aorta.

Succesful implantation of the allograft with the subcoronary technique is highly related to the surgeons' experience and a learning curve of the surgical technique has been reported[15,16]. Therefore, the results from the first 10 operated patients with the subcoronary implantation technique of each individual surgeon were considered to represent the learning curve. There were three surgeons included.

Surgical procedures were performed using standard cardiopulmonary bypass with moderate hypothermia, myocardial protection with crystalloid cardioplegia (St. Thomas solution), and topical cooling. Deep hypothermia and circulatory arrest was used in selected patients with ascending aorta or arch pathology.

Allograft characteristics

One hundred and forty-eight cryopreserved aortic allografts were supplied by the Heart Valve Bank, Rotterdam, through Bio Implant Services Foundation, The Netherlands. Three cryopreserved allografts were supplied from the National Heart Hospital, London and 3 allografts from the Karolinska Homograft Bank, Stockholm, Sweden. The aortic allografts were prepared from hearts of heart-beating (n=118) or non heart-beating donors (n=36). Cryopreservation of the implanted allograft valves was initially carried out with glycerol solution (n=32) and in recent years with dimethylsulfoxide (DMSO) solution (n=122). The technique for dissection, quality coding, decontamination and cryopreservation has been reported before[17]. The mean donor age was 37 years (range, 13 to 57 years). No attempt was made to achieve ABO bloodtype or sex matching.

The mean internal diameter of the allografts was 23.4 mm (range, 19 to 28 mm). The inner allograft diameter was ideally 2 mm smaller than the patients' annulus diameter measured from their preoperative echocardiograms.

Echocardiographic study

Serial precordial echocardiography was performed from 1987 till 1993, to assess both the morphology and function of the aortic allograft valve. The severity of aortic regurgitation was estimated by the jet length method on a scale of 0 to 4; grade 0 represented no regurgitation, grade 1: the jet was limited to the left ventricular outflow tract, grade 2: the jet was visible extending between the left ventricular outflow tract and halfway the left ventricular cavity, grade 3: the jet reached halfway the ventricular cavity, grade 4: the jet reached more than halfway the left ventricular cavity. The depth to which the regurgitation jet extends into the left ventricular cavity allows a semiquantitative assessment, however, this technique may overestimate the severity of the regurgitation[18,19].

Therefore, since January 1993 the severity of aortic regurgitation was also estimated by measuring the ratio of the maximal regurgitant jet diameter to the systolic left ventricular outflow tract diameter directly under the aortic valve in the parasternal long-axis view (jet diameter method)[18].

The echocardiographic examinations were initially performed with different echocardiographic equipment. From January 1993 all examinations were performed on a Vingmed CFM 750 ultrasound system (Vingmed, Trondheim, Norway) with a 3.25 MHz transducer by two experciened technicians to limit intermachine and interobserver variability[20]. During color Doppler examination of the left ventricular outflow tract for regurgitant flow signals, the gain is standardized by starting at low gain and increasing until white noise appears in the left ventricular cavity. The flow velocity is set between 0.7 and 1.0 m/s, depending on the depth. The threshold of the flow velocity is always set at 0.25 m/s.

Diameters are measured on-line on the video screen from frozen images by planimetry using a trackball. The mean values of measurements from two cardiac cycles are noted.

Postoperative echocardiographic examinations were scheduled at 6 months, at 1 year and at yearly intervals thereafter.

Follow-up

The median duration of follow-up for the hospital survivors was 4.2 years (range, 1 month to 7.7 years) after subcoronary implantation, 2.1 years (range, 1 month to 6.3 years) after allograft root replacement and 2.1 years (range, 1 month to 8.2 years)

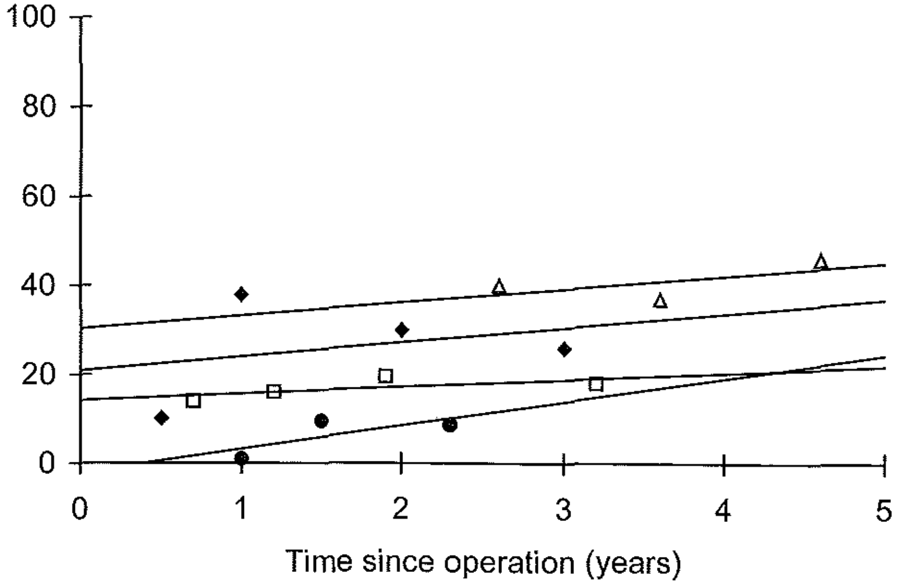

Figure 1. Hierarchical linear models estimate a regression line with an intercept and slope for individual patients. The intercepts reflects the initial severity of aortic regurgitation and the slope reflects the change of its severity, as illustrated for four individual patients.

after autograft root replacement. The closing date for inclusion of events and echocardiographic examinations was July 1, 1996.

Statistical analysis

Survival and freedom from reoperation for aortic valve failure were analyzed according to the method of Kaplan-Meier[21]. The survival of a patient started at the time of allograft or autograft implantation and ended at death (event) or at last follow-up (censoring). The analysis of allograft or autograft survival started at time of implantation and ended with allograft or autograft failure (reoperation, valve related death) or at the last follow-up (censoring). The differences between curves were evaluated with the log-rank test.

After univariate analysis a multivariate analysis of patient survival and aortic valve related reoperation was performed with the proportional hazard regression model as described by Cox[22]. We applied backward stepwise selection with $p<0.10$ for inclusion of the most important variables in the Cox model.

The echocardiographic data were analyzed by using a multi-level hierarchical linear model (HLM)[23]. This model is suitable for a statistically correct analysis of different numbers of repeated echocardiographic examinations in the same patient, that were not performed at exactly the same intervals since operation. It provides a regression line with an intercept and slope for individual patients. The intercept reflects the initial severity of aortic regurgitation and the slope reflects the change of its severity during follow-up. Examples of individual regression lines are shown for 4 patients in Figure 1. The HLM calculates standard deviations to reflect the variability within and between patients during follow-up, and allows for evaluation of covariables for the intercept and slope of the regression lines.

These covariables were examined by complete case analysis. Patient characteristics included age at operation (≥ 40 year, n=133) , preoperative hypertension (n=26), preoperative left ventricular function, previous aortic valve surgery (n=37), aortic root pathology (n=70) and urgent operation (n=14). Surgical variables included subcoronary implantation technique (n=83) versus aortic root replacement with allograft or autograft (n=123) and the learning curve of the surgeon (n=30). Valve characteristics included cryopreservation method (glycerol, n=32, DMSO, n=122), allograft diameter (≥ 25 mm, n=32), quality code (good, n=125, moderate, n=78, missing, n=3), donor age (≥ 40 year, n=73) and type of donor (heart-beating, n=118, non heart-beating, n=36).

The following definitions for covariables were used. Hypertension: diastolic pressure of > 95 mmHg or medically treated. Urgent operation: operation within 24 hours after examination by the surgeon. Quality code: based on macroscopic allograft characteristics, and qualified as good or moderate (poor quality valves were discarded). Heart beating donor: time between circulation stop and cardiectomy less than 2 hours. The remaining valves were defined as from non – heart beating donors. The square root of the jet diameter ratio was calculated to minimize the influence of outliers and to normalize the distribution.

Results

Patient Survival

The hospital mortality rate for subcoronary impantation was 4.9% (4 of 82 patients), for aortic root replacement with an allograft 4.3% (3 of 70 patients) or an autograft 3.8% (2 of 52 patients), respectively. The 5-year patient survival after subcoronary implantation and aortic root replacement with allograft or autograft was 81% (95% CL 72 to 89%), 94% (95% CL 92 to 97%) and 96% (95% CL 93 to 99%), respectively. Hospital mortality and 5-year patient survival did not differ significantly among the groups (p=ns).

Reoperation

The 5-year freedom from aortic valve related reoperation after the subcoronary implantation was 86% (n=10, 95% CL 82 to 90%) and for aortic root replacement with an allograft 94% (n=2, 95% CL 89 to 98%) or autograft 97% (n=1, 95% CL 94 to 99%), respectively. The reoperations after subcoronary implantation were performed

Table 1. Freedom from aortic valve related reoperation at 5 years stratified for covariables

Analyzed variables	Freedom from aortic valve related reoperation	95% CL	HR Univariate	HR Multivariate
Type of operation;				
SCA (n=83)	86%	78 – 94%		
Root (n=123)	95%	89 – 99%	3.3 (0.9 – 12.3)	4.1 (0.7 – 21.8)
Cryopreservation method;				
Glycerol (n=32)	80%	66 – 94%		
DMSO (n=122)	92%	84 – 99%	3.9 (1.0 – 9.2)	--
Learning curve;				
Unexperienced (n=30)	84%	74 – 94%		
Experienced (n=176)	95%	89 – 99%	0.3 (0.1 – 0.9)	0.2 (0.04 – 1.0)
Allograft diameter;				
19-25 mm (n=32)	93%	87 – 99%		
> 25 mm (n=122)	77%	62 – 92%	3.3 (1.1 – 10.1)	3.8 (1.1 – 13.1)

SCA; subcoronary implantation technique

for severe aortic regurgitation in 9 patients and for late aortic stenosis in one patient. Two reoperations after allograft root replacement were performed for a pseudoaneurysm at the proximal anastomosis without severe aortic regurgitation. One autograft was replaced for severe aortic regurgitation due to recurrent acute rheumatic fever[24].

The freedom from aortic valve related reoperation was very similar after aortic root replacement with an allograft or autograft. Therefore, the results concerning reoperation after allograft root and autograft root replacement were taken together for comparison with the subcoronary group. It appeared that the 5-year freedom from aortic valve related reoperation was significantly lower in the subcoronary group (86% vs. 95%, p=0.05).

Multivariate analysis determined the surgeons' learning curve and an allograft diameter larger than 25 mm as risk factors for reoperation (Table 1).

Aortic regurgitation on color Doppler echocardiographic analysis

In the analysis of the jet length and jet diameter method we found an initial aortic regurgitation (intercept 1.11, 0.15 respectively) for all implanted valves, allograft or autograft, with a moderate progression of the regurgitation severity (slope both 0.09) during follow-up (Table 2). Patients with root replacement were considered as one group, since differences were very small between those with an allograft or an autograft implanted, when analyzed with the jet length or jet diameter method.

Table 2. Hierarchical linear model analysis for aortic regurgitation on color Doppler echocardiography

	jet length method				jet diameter method			
Variables	Intercept	p-value	Slope	p-value	Intercept	p-value	Slope	p-value
All valves (n=206)	1.11	<0.001	0.09	<0.001	0.15	<0.001	0.09	<0.001
Type operation: SCA versus Root	Δ=+0.42	0.01	Δ=+0.03	0.54	Δ=+0.11	0.004	Δ=-0.003	ns
Learning curve vs. more experienced	Δ=+0.38	0.05	Δ=-0.03	0.50	Δ=+0.03	ns	Δ=-0.02	0.15

SCA; subcoronary implantation technique, ns; not statistical significant

Jet Length Method

Unavailable for echocardiographic analysis were 8 patients who died in hospital, 6 patients who were lost to echocardiographic follow-up and 2 patients with a poor quality of echocardiographic examination. Also, 16 patients with an echocardiogram within 6 months after the operation were excluded. This selection left 578 echocardiographic examinations of 206 implanted human tissue valves in 204 patients available for analysis. One hundred seventy-two (84%) patients had one or more echocardiograms during a mean follow-up of 2.2 years (range, 0.5 to 7.2 years). Two or more echocardiograms were available in 143 patients (70%). The number of echocardiographic examinations was 3.4 on average, with a range from 1 to 8 echo's.

Mean initial aortic regurgitation was 1.11 grade and an average yearly increase of 0.09 grade was found. The severity of aortic regurgitation varied considerable during follow-up within patients (standard deviation around the regression line: 0.39). The differences between patients were, however, larger (standard deviation of differences between the individual regression lines: 0.74).

Valves implanted with the subcoronary implantation technique showed more initial aortic regurgitation than those implanted with the root replacement technique (Δ intercept=0.42, p<0.01, Table 2). The severity of aortic regurgitation remains relatively stable during the observation period, given a rise of only 0.1 grade/year after

Table 3. Hierarchical linear model analysis for aortic regurgitation adjusted for type of operation

	jet length method				jet diameter method			
Variables	Δ Intercept	p-value	Δ Slope	p-value	Δ Intercept	p-value	Δ Slope	p-value
Age at operation	0.11	ns	0.06	ns	0.04	ns	0.01	ns
Hypertension	0.35	0.08	-0.13	0.06	0.29	0.13	-0.14	0.04
LV function	-0.05	ns	0.12	0.04	0.02	ns	-0.01	ns
Previous AVR	-0.06	ns	-0.04	ns	-0.09	0.07	0.04	0.01
Aortic root pathology	-0.05	ns	-0.04	ns	-0.05	0.14	-0.02	ns
Urgent operation	-0.04	ns	0.08	0.14	0.04	ns	0.07	0.16
Cryopreservation method	0.36	0.04	-0.01	0.08	0.05	ns	0.002	ns
Allograft diameter	0.14	ns	0.02	ns	0.17	ns	0.02	ns
Quality code	-0.02	ns	0.02	ns	0.17	ns	0.02	ns
Donor age	0.001	ns	0.001	ns	-0.001	ns	0.001	ns
Type of donor	0.11	ns	-0.01	ns	0.10	ns	0.001	ns

LV; left ventricular, AVR; aortic valve replacement, ns; not statistical significant

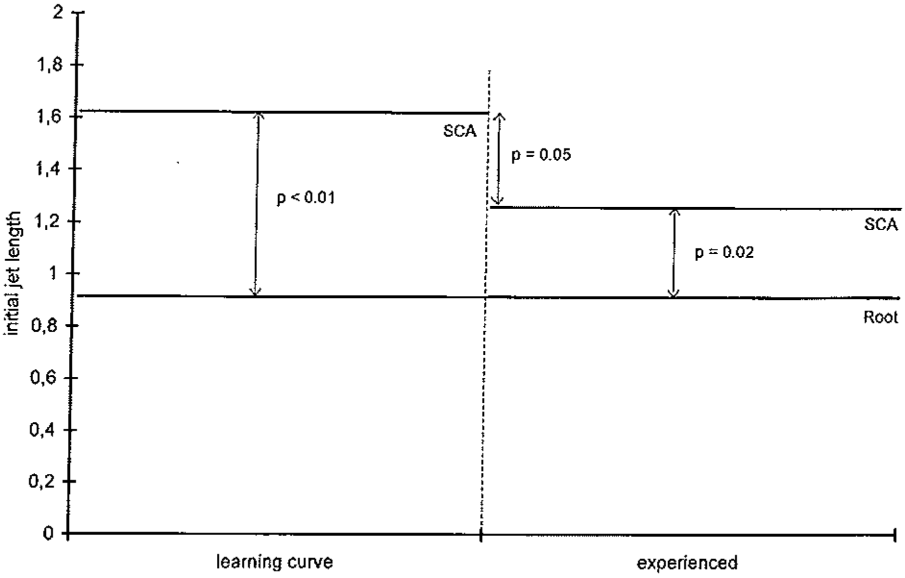

Figure 2. The influence of the surgeons' learning curve on the initial severity of aortic regurgitation analyzed by the jet length method.

subcoronary implantation and 0.07 grade/year after root replacement techniques. This difference in slopes of 0.03 grade/year was not statistically significant ($p>0.5$).

We analyzed patients operated during the learning phase of three surgeons' first 10 patients and patients operated upon later within the subcoronary implantation group. The initial aortic regurgitation (intercept 1.62) was higher during the surgical learning phase than in the later period ($p=0.05$). A graphical representation of the effects of the learning phase and the implantation technique on initial aortic regurgitation is shown in Figure 2. This analysis was not made for the root replacement group, since no learning curve was expected nor was it identified in the data. The initial aortic regurgitation was less after root replacement (intercept 0.92, $p<0.05$), also when compared to the subcoronary implantation technique during the more experienced phase. We observed no differences between the slopes according to surgical experience or implantation technique.

Further analysis of covariables was undertaken while controlling for potential confounding effects of the implantation technique. This was done by including the type of operation as a covariable in the model (Table 3). Valves preserved with glycerol showed more initial aortic regurgitation compared to valves preserved with DMSO. Minimal progression of aortic regurgitation was detected in patients with good functioning left ventricles.

Jet diameter method

From March 1993 to July 1996, 404 echocardiographic examinations were available in 163 patients (80%) for evaluation of the severity of aortic regurgitation by the jet diameter method. The same patients as mentioned in the jet length analysis were unavailable for analysis. Also unavailable for analysis were 2 patients who died in hospital, 6 patients with a reoperation for allograft failure before 1993 and one patient was lost to follow-up after 1993. The mean duration of this echocardiographic follow-up was 1.6 years (range, 6 months to 3 years).

One hundred and thirty patients (64%) had two or more echocardiograms during follow-up. The mean number of echocardiographic examinations with the jet diameter method was 2.5 (range, 1 to 5 echo's). Mean initial aortic regurgitation was 0.15 with an average yearly of 0.09. The standard deviation for the severity of aortic regurgitation was 0.09 within the individual patients and 0.18 between patients.

The subcoronary implanted valves had more initial aortic regurgitation than after root replacement (Δ intercept=0.11, p=0.004, Table 2). No difference in the progression of aortic regurgitation between the implantation technique groups was seen during the observation period. The surgeons' learning curve for the jet diameter method could not be analyzed since this period had passed before the collection of these echocardiographic data was started. The data on aortic regurgitation as determined with the jet diameter method are shown in Figure 3a and 3b. The collected data of all operated patients are plotted in these figures with the average regression lines from the HLM analysis for the subcoronary group (Figure 3a) and the root replacement group (Figure 3b). The influence of covariables was analyzed while correcting for the confounding of operative technique by inclusion of implantation technique in the regression models (Table 3). No significant effects of covariables were observed, except less progression of aortic regurgitation during follow-up in patients with preoperative hypertension and in patients with a previous aortic valve replacement (p=0.04, p=0.01 respectively).

Discussion

Aortic valve replacement with human tissue valves in patients with aortic valve or root disease is the preferred intervention in the younger age group. This is based on the reported excellent hemodynamic performance, avoidance of the need of lifelong anticoagulation, a low risk of thromboembolism and reduced infectious complications[1-12]. There seems to be an improved durability compared to the bioprosthesis. Nonetheless, human tissue valves have a limited durability that may necessitate reoperation[1-12].

An important determinant of durability is the method of preservation of the aortic allografts. In recent years, the techniques that apply chemical preservation, irradiation and freeze drying have been replaced by immediate transplantation or by

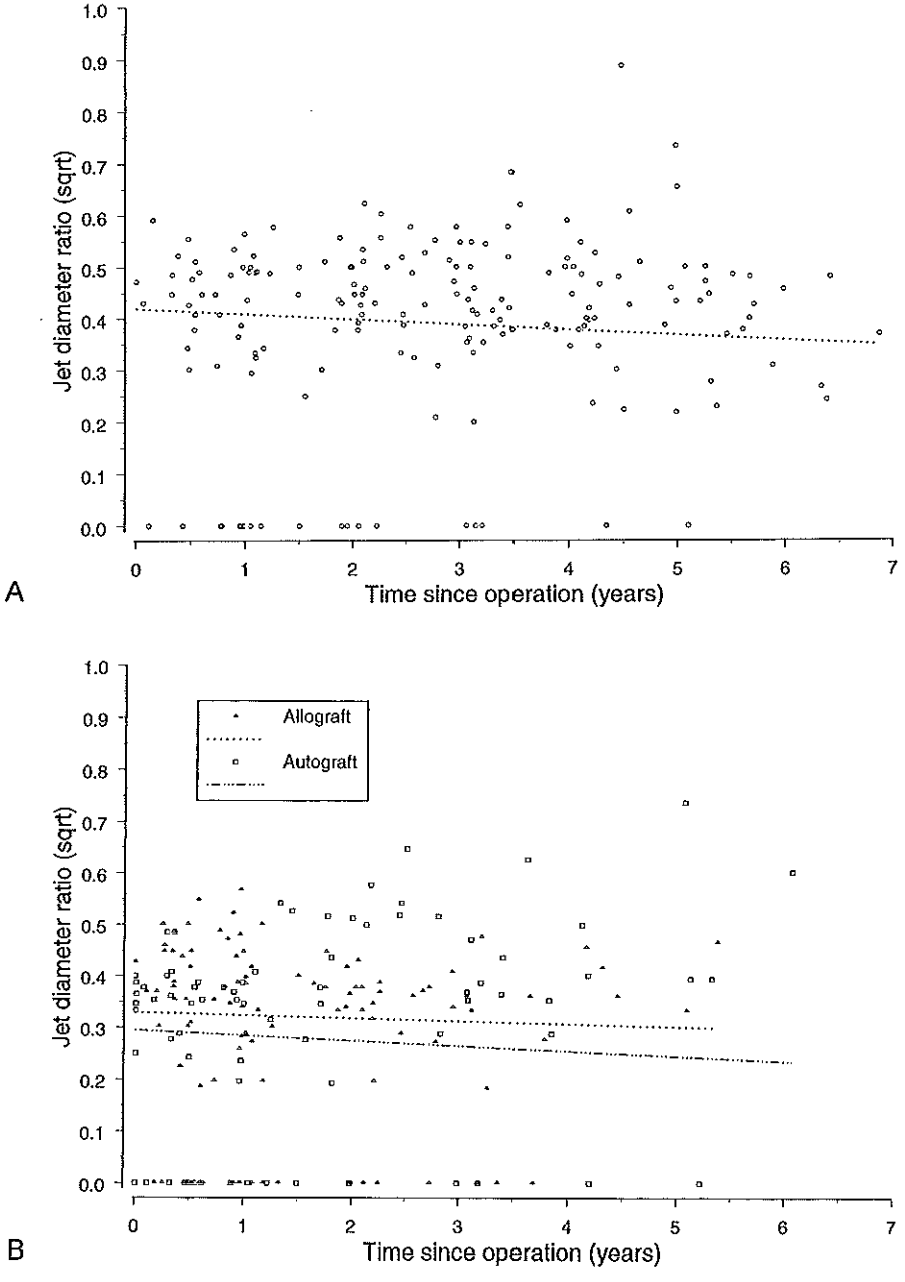

Figure 3. The data on aortic regurgitation after the subcoronary implantation (A) and root replacement technique (B) measured by the jet diameter method during follow-up. The dotted line represents the regression line calculated by the hierarchical linear model.

fresh-wet storage in an antibiotic solution or cryopreservation. As a consequence of these changes the durability of the valves has improved considerably[1-4,7,25]. Several studies have shown other important determinants of durability, such as young recipient age (< 30 years)[4,7], previous xenograft valve implantation[7], donor valve age (> 55 years), large aortic root diameter[1] and the surgeons' learning curve[15,16]. Another determinant, which is still under debate for both allograft and autograft valves, is the choice of the surgical technique; subcoronary implantation or aortic root replacement. Reports on early and late human tissue valve function should take into account these risk factors for valve degeneration[13].

The most common used end point of valve dysfunction is reoperation, which is rather crude and may underestimate the incidence of valve failure. Patients with clinically well tolerated moderate-severe aortic regurgitation do not necessarily undergo a reoperation. Echocardiographic examinations may therefore be useful to assess the severity of aortic regurgitation. Valve dysfunction can then be expressed as the combined endpoint of reoperation and moderate-severe aortic valve regurgitation. This information can be analyzed in a time dependent model using the Kaplan-Meier method to estimate freedom of valve failure curves. The Kaplan-Meier method is not ideal for analysis of echocardiographic data for the following reasons[21]. Time of follow-up should be used as a continuos variable. However, echocardiographic data are usually available within a certain time frame and data after specified intervals of the operation may be incomplete. More importantly, the use of the Kaplan-Meier method can be misleading in the analysis of classified echocardiographic data. The severity of aortic regurgitation in each patient is variable over time. In our study this variability can be caused by the use of different echocardiographic equipment before 1993 and the individual changes of the patients' hemodynamic condition. Therefore, the censoring of a moderate-severe aortic regurgitation may occur too early. Data on patients with less than moderate-severe and severe aortic regurgitation are not used to observe changes in regurgitation (reflecting late valve degeneration) over time.

The hierarchical linear model, as used in our study, takes into account both the follow-up time and changes in the severity of aortic regurgitation[23]. It determines the initial severity of aortic regurgitation and changes in its severity over time, reflecting the behavior of implanted human tissue valves. The influence of interrelated determinants of the durability of human tissue valve can be studied with changes in intercept and slope as endpoints.

The durability of human tissue valves in the aortic position is generally represented by the freedom from reoperation. One determinant of durability that remains unresolved, is the implantation technique: subcoronary implantation or root replacement? Some authors favor aortic root replacement over subcoronary implantation, because they hypothesize that early aortic valve regurgitation is minimized by the preservation of the aortic root geometry as a functional unit[2,3,26,27]. Other surgeons are less concerned with reoperation for aortic incompetence after subcoronary implantation and prefer to avoid more radical root resection and the late risk of aortic root calcification with progressive loss of radial extensibility[28,29]. The calcified root may cause late aortic regurgitation and the reoperation in this setting is more complicated[30].

This series confirms our previous findings of the important influence of the surgeons' experience on the high incidence of reoperation after subcoronary implantation compared to root replacement[16]. A learning curve for the subcoronary implantation technique is not a uniform finding in the surgical literature[8,15]. However, in clinics with a resident training program, this is an important disadvantage of using the subcoronary implantation technique compared to the aortic root replacement.

In parallel with the findings based on the incidence of reoperation, more initial aortic regurgitation during echocardiographic examination was found after subcoronary implantation. The surgeons' experience is an important risk factor and a learning curve is apparent. Even after this learning period, more initial aortic regurgitation was detected on echocardiography with the subcoronary implantation technique. This is also a strong argument in favor of the aortic root replacement technique.

Small progression of the severity of aortic regurgitation, as expressed by the slope of the regression line, was found during this medium term follow-up study of aortic allografts and autografts. Progression of aortic regurgitation was not influenced by implantation technique. Hypertension and normal preoperative left ventricular function tended to be associated with less progression of aortic regurgitation. Increased progression of aortic regurgitation severity in patients with a previous aortic valve replacement was found. A relation between this progression and previous xenograft replacement of the aortic valve, as described by Yacoub, was not apparent[7]. In our study, however, only four patients had a previous xenograft replacement in aortic position. The analysis of other interrelated covariables for late valve degeneration is likely to be demonstrated when longer follow-up time has elapsed.

During our echocardiographic follow-up study, the grading of aortic regurgitation severity by the jet length method was complemented by the more advanced jet diameter method. The consequences of this choice are the differences in follow-up time interval. Despite these differences, there is agreement between echocardiographic analysis with the jet length and jet diameter method. In our study the aortic allografts and autografts, used for aortic root replacement were considered as one group. We are well aware that these valves have different histological and morphologic characteristics, but the hemodynamic performance of both valves is comparable during this medium term follow-up.

In summary, this series demonstrates that the aortic root replacement technique is superior to the subcoronary implantation technique with regard to valve regurgitation. The surgeons' learning curve is an important limitation for the subcoronary implantation technique. Also after this learning period has passed there is more initial aortic regurgitation after the subcoronary implantation technique compared to aortic root replacement. The progression of the aortic regurgitation is small for both implantation techniques during medium term follow-up. In our hospital the subcoronary implantation technique is no longer in use and the aortic valve is preferably replaced by using an aortic allograft or pulmonary autograft root.

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Discussion

Chapter 8

The value of echocardiography in follow-up of human tissue valves in aortic position: Discussion

Validity and reproducibility of echocardiography

The third and fourth chapter of this thesis provide the evaluation of the validity and reproducibility of the color Doppler echocardiographic quantification method for assessment of aortic regurgitation severity. Quantification of aortic regurgitation severity after human tissue valve implantation is desirable to monitor early and late valve dysfunction. Color Doppler echocardiography is an attractive non-invasive method for serial evaluation of patients with aortic regurgitation. In clinical practice, different methods are used for the quantification of severity of aortic regurgitation and they all have their limitations. In chapter three the agreement between the color Doppler quantification method and angiography was assessed in our hospital. The grading of the severity of aortic regurgitation by scoring the length of the regurgitant jet in the left ventricle showed a good correlation with the reference method; angiography. However, as known form previous studies[1,2] the jet length method may overestimate its severity, because it is largely dependent on systemic afterload and regurgitant orifice morphology. We found in our study also an underestimation of aortic regurgitation severity as scored by the jet length method.

With reference to previous studies[1,3-5] we found that the jet diameter or area of the regurgitant jet relative to the size of the left ventricular outflow tract is closely related to the severity of aortic regurgitation as determined by angiography. Despite a good correlation between the jet diameter and area method with angiography a subdivision of four individual grades of aortic regurgitation severity could not be performed. The jet diameter method seems to be a valid method for discrimination between mild and severe aortic regurgitation. The cut-off value was found to be a jet diameter–left ventricular outflow tract diameter ratio of 20%. This value is slightly lower than the cut-off values as determined by Dolan[3]. He found a cut-off value for the jet diameter method between 25% and 40% to distinguish between mild and severe aortic regurgitation. In Chapter 6 the threshold values as defined by Perry and associates were applied[1]. The jet diameter ratios were mainly clustered around the threshold between the grade 1 and grade 2. A small shift of these threshold values had major consequences for interpretation of echocardiographic data. Although grading of jet diameter ratios is useful in clinical practice, it is less valid for the determination of the aortic regurgitation severity during a serial echocardiographic follow-up study. Also from statistical point of view, the original jet diameter ratios are preferred over grouping of data.

Despite a good correlation between the angiographic grading and the jet area method, a practical discrimination between mild and severe aortic regurgitation is impossible. Furthermore, the jet area method is limited by technical difficulties. The study in Chapter 4 shows the large interobserver and intraobserver variability for the jet area-left ventricular outflow tract area ratio measurements. This variability is caused by the inaccuracies of tracing of the areas with trackball and the selection of the still frame by the observers. The agreement for the jet area and left ventricular outflow tract area showed a small bias, but a large variance. On the other hand, both the interobserver and intraobserver variability for the jet diameter and left ventricular outflow diameter measurements showed a very close agreement.

Perry and associates[1] described that the jet area method is more closely related to the severity of aortic regurgitation than the jet diameter method. The jet area method was considered to be the best technique. Nevertheless, previous conclusions were based on correlation coefficients rather than the reproducibility of the quantification method for the severity of aortic regurgitation. We found also comparable good interobserver and intraobserver correlations coefficient for the LVOT-jet diameter and LVOT-jet area measurements (0.82, 0.85, 0.74 and 0.92). However, the reproducibility of measurements was assessed by the method of Bland and Altman[6], that compares the whole range of values between two variables and gives information about the differences between two variables. The study in Chapter 4 shows a better reproducibility of LVOT-jet diameter compared to the LVOT-jet area measurement.

Based on good agreement between the jet diameter method with angiographic grading and high reproducibility of the measurement of jet diameter and LVOT diameter, this method was preferred in the follow-up of the individual patient (Chapter 6 and 7) over the jet area method for estimation of aortic regurgitation from color Doppler images.

Human tissue valves: mortality and reoperation

After improvement of the allograft durability by adoption of sterilization methods and publications of the first good long-term clinical results[7-9], we started to use allografts and autografts for aortic valve replacement in 1987. The excellent hemodynamic performance, avoidance of the need for lifelong anticoagulation, low risk of thrombo-embolism and reduced infectious complications are advantages compared with mechanical valves.

The subcoronary implantation technique was mainly used in patients with aortic valve pathology and intact aortic root. The aortic allograft valves were initially implanted with scalloping of each sinus of Valsalva. Subsequently, the subcoronary implantation technique was performed with preservation of the aortic wall of the noncoronary sinus. This technique was introduced by Ross[10] to avoid anatomic malpositioning of valve leaflets.

The aortic root replacement technique was mainly used in patients with aortic valve disease associated with major aortic root pathology. Although the long-term results of Ross[11] with subcoronary implantation of autografts were good, aortic valve replacement with the pulmonary autograft was only performed by using the root replacement technique. A possible discrepancy between the aortic annulus diameter and pulmonary autograft diameter is more critical with the subcoronary implantation technique compared to the root replacement technique. Overmore, in neonates the subcoronary implantation technique is not feasible.

The reproducibility of subcoronary implantation technique and aortic root replacement by using an aortic allograft or autograft is shown by the low rates of early mortality in our series (Chapter 6 and 7). The causes of death were cardiac failure unrelated to allograft or autograft failure. Also during follow-up no cases of valve related death were found and no risk factors for mortality were identified. Two patients with Marfan's syndrome died after aortic root replacement with a pulmonary autograft. Although this condition was not the cause of a valve related death, Marfan's syndrome is probably not a suitable condition for aortic root replacement using a pulmonary autograft because the disease affects the pulmonary artery as well[12].

The incidence of valve related reoperation after aortic root replacement with an allograft or autograft was significantly lower compared with the subcoronary implantation technique. The results concerning reoperation after the allograft root and autograft root replacement were taken together in chapters 6 and 7 for comparison with reoperations rates after subcoronary implantation. We were aware that the aortic allograft and autograft have different histological and morphologic characteristics, but the hemodynamic performance of both valves is comparable at medium term follow-up, as evidenced by the similar incidence of valve related reoperation for both valve types.

Reoperation after subcoronary implantation was mainly performed for severe aortic regurgitation. Paravalvular leakage was the main reason for early reoperation and was caused by dehiscence of sutures. A combination with aortic stenosis was possible if the aortic annulus was displaced inwards. The subcoronary implantation technique was initially used in patients with active endocarditis at the time of implantation. However, these patients were predisposed for dehiscence of sutures, because of involvement of the aortic root in the infectious process. Therefore, the aortic root replacement technique was subsequently used in patients with active endocarditis.

Pseudoaneurysm at the proximal anastomosis was the cause of reoperations after allograft root replacement. Pseudoaneurysms are due to partial dehiscence at the proximal or distal suture line. Careful suturing of the proximal and distal anastomosis is necessary for avoiding premature reoperation. Reoperation after root replacement with an autograft was necessary for a patient with recurrent acute rheumatic fever destroying the autograft[13]. Aortic root replacement with an autograft is contraindicated in patients with chronic juvenile rheumatoid arthritis[14,15]. In patients with acute rheumatic fever autograft procedure is relatively contraindicated, depending on the adequacy of antibiotic prophylaxis for the disease. Our concern corresponds with the results of Kumar and associates[15,16], who operated 48 patients with rheumatic fever. Three patients had to be reoperated despite continuous use of antibiotic prophylaxis.

Chapters 6 and 7 indicate that the higher incidence of reoperations after subcoronary implantation compared to root replacement is influenced by the surgeons' experience. The root replacement technique is a firmly established surgical technique as shown by the use of other types of valved conduits. Compared to subcoronary implantation, the matching of allograft size with the recipients' annulus is less critical, and implantation of the grafts as a functional unit is less prone to surgical error[17]. A learning curve for the subcoronary implantation technique, however, is not a uniform finding in the surgical literature[18-20]. In clinics with a resident training program, the learning curve is an important disadvantage of using the subcoronary implantation technique.

Human tissue valves: echocardiographic follow-up

Two-dimensional and color Doppler echocardiography was performed as non-invasive tool for the follow-up to assess allograft-specific pathomorphology and severity of aortic regurgitation. Patients with clinically well tolerated moderate-severe aortic regurgitation or specific pathomorphology, like paravalvular leakage, may not undergo reoperation. Therefore, reoperation may underestimate the incidence of valve failure.

Chapter 5 confirms the favorable low transvalvular gradients of aortic allograft after both subcoronary implantation and root replacement. The mean peak velocity across the aortic allograft after subcoronary implantation was 1.8 m/s and after root replacement 1.4 m/s. This peak velocity is comparable with a normally functioning native aortic valve (1.3 m/s)[21]. Only one patient required reoperation for severe aortic stenosis after the subcoronary implantation technique. The explanted valve leaflets showed severe calcification. An other patient after the subcoronary implantation technique has moderate aortic stenosis, but is in a clinical good condition after 5.6 years of follow-up.

A pseudoaneurym at the proximal or distal anastomosis was detected in 3% of all patients with an allograft. Paravalvular leakages were found in 15% of patients after subcoronary implantation. Reoperation for paravalvular leakage was required in 5% of the patients. The incidence of echo-free spaces around allografts on echocardiography differs from the study of Oechslin and associates[22]. They described pseudoaneuryms in 73% of patients after the subcoronary implantation and root replacement. In their study in most patients the root replacement technique was performed as an inclusion cylinder and in a few patients as a freestanding root. The difference in incidence of echo-free spaces can only in part to be explained by the different implantation technique.

The most striking observation in chapter 5 is the difference in incidence of eccentric jets between the subcoronary implantation and root replacement. The low incidence of eccentric jet patterns after the root replacement technique supports the concept of a better preservation of the geometry of the donor leaflets with less turbulent flow during closure. The learning curve, as described in chapter 6 and 7 might have influenced these results, and the influence on late valve function remains unclear. Chapter 5 also shows the high incidence of sharply angulating jets in allografts, especially after the subcoronary implantation technique. These jets originate centrally and have an initial eccentric trajectory at the level of the leaflets, hit the left ventricular outflow tract wall and are thereafter projected into the left ventricle. These eccentric jets are relevant for the quantification of aortic regurgitation and were noticed preciously by Jaffa and colleagues [23]. In addition, multiple jets may be confusing for quantification of the severity of the regurgitant jet. In our study, the size of a regurgitant jet was measured just below the aortic valve or in case of eccentric jets at aortic valve level to avoid an overestimation of the jet size. The sizes of the multiple jets were added up.

The progression of aortic regurgitation over time after allograft or autograft implantation is described in chapter 7. A hierarchical linear model was used to analyse serial echocardiographic examinations. This model takes into account the variable of follow-up time and changes in the severity of aortic regurgitation. The use of different echocardiographic equipments before 1993 and the individual changes of the patients' hemodynamic condition can produce variability in serial measurements in the same individual. The use of the Kaplan-Meier method may be misleading in the analysis by censoring too early for moderate-severe aortic regurgitation[24]. The hierarchical linear model determines the initial and the changes in the severity of aortic regurgitation. The influence of interrelated determinants for valve failure was studied with intercept and slope as endpoints.

In parallel with the findings based on the incidence of reoperation, as described in chapter 6 and 7, more initial aortic regurgitation was found after subcoronary implantation. The learning curve for the subcoronary implantation technique, as shown in chapter 6, was also apparent in the echocardiographic examinations. Even after passing the individual surgeons' learning phase, more aortic regurgitation was detected after using the subcoronary implantation technique. Only a minimal progression of the severity of aortic regurgitation was found during the medium term follow-up. An influence of implantation technique on the minimal progression was not identified.

With reference to previous studies, we hypothesize that early aortic valve regurgitation is minimized by the preservation of the aortic root geometry as a functional unit[17,25-27].

Conclusions

Two dimensional and color Doppler echocardiography is a useful non-invasive tool for the follow-up of patients with an allograft or autograft. The application of the jet diameter method for the quantification of aortic regurgitation severity has a good correlation with angiography and furthermore has a high reproducibility. The aortic root replacement technique is superior to the subcoronary implantation technique with regard to the allograft-specific pathomorphology, incidence of reoperation, and the severity of valve regurgitation. The surgeons' learning curve for the subcoronary implantation technique is an important limitation. Progression of aortic regurgitation is minimal for both implantation techniques. Other determinants of durability were not apparent during medium term follow-up. In our hospital the subcoronary implantation technique is no longer employed and the aortic root is preferably replaced by an aortic allograft or pulmonary autograft.

Future research

At present, the aortic allograft and pulmonary autograft seem to be good options for aortic valve or root replacement. The root replacement technique is preferred, but longer follow-up is needed to detect other determinants of durability. A definitive statement regarding the use of aortic allograft or pulmonary autograft in aortic position is only possible after long-term results have become available. The incidence of reoperation and severity of aortic regurgitation are the ultimate parameters.

Echocardiographic follow-up of the valves is only useful when all examinations are performed according to a predetermined protocol. The intermachine and interobserver variability has to be limited. Also, the echocardiographic quantification method for the severity of aortic regurgitation should be evaluated in each hospital. Despite its limitations, angiography is still the reference for the echocardiographic quantification method for severity of aortic regurgitation. Other non-invasive methods, like magnetic resonance imaging, should be assessed for quantification of severity of aortic regurgitation.

The definition of assumed aortic allograft or autograft failure, i.e. either reoperation or death, or clinical presence of valve failure as assessed by echocardiographic aortic regurgitation or physical examination, needs to be re-evaluated. A new definition of assumed valve failure that takes factors like for instance progression of aortic severity or clinical symptoms over time into account, is needed.

Future research on preservation techniques, patient and surgery related variables influencing allograft function should be conducted. Good teamwork with the department of pathology and immunology is desirable to obtain more information about the process of valve degeneration and the influence of determinants on valve durability.

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Appendices

Summary

Human tissue valves are increasingly used for aortic valve or root replacement, but have a limited durability, influenced by several interrelated determinants. The durability of these valves is reflected by the end-points of valve related reoperation and mortality. These end-points, however, are insensitive for determining the valve function during follow-up. Echocardiography allows non-invasive evaluation of the process of valve degeneration, that has important consequences for patient counselling and research.

Chapter 1 and *Chapter 2* provide an introduction of this thesis describing the history of the application of human tissue valve in cardiac surgery and the rationale for the assessment of human tissue valve function during follow-up. In particular, the application of color Doppler echocardiography as tool for the assessment of valve function is described.

Chapter 3 provides the agreement between the color Doppler echocardiographic grading methods and angiography in the assessment of aortic regurgitation severity. The assessment of the ratio of jet diameter to left ventricular outflow tract diameter (jet diameter method) seems to be a valid method for discrimination between mild and severe aortic regurgitation, and is in contrast with the assessment of the ratio of jet area to left ventricular outflow tract area (jet area method).

Chapter 4 provides the reproducibility of the jet diameter and jet area method. Color Doppler echocardiographic examinations of 62 patients with isolated aortic regurgitation after human tissue valve implantation were examined. The interobserver, intraobserver and interframe variability showed a close agreement for the jet diameter and left ventricular outflow tract diameter method. The agreement for the jet area and left ventricular outflow tract area method showed a small bias, but a large variance. The reproducibility of the jet diameter method is better than the jet area method and is more accurate to assess the severity of aortic regurgitation from color Doppler images.

Chapter 5 is a description of valvular pathomorphology findings and color Doppler jet patterns in patients after aortic allograft placement with either the

subcoronary implantation or root replacement technique. The incidence of paravalvular leaks and eccentric regurgitant jets was higher with the subcoronary implantation (41%) compared with the root replacement (11%). These findings support the validity of the concept of preservation of the geometry of the aortic root after root replacement.

Chapter 6 is a description of the influence of the surgeons' learning curve on the incidence of reoperation and the severity of postoperative aortic regurgitation assessed by color Doppler echocardiography. In this series, the subcoronary implantation technique was used in 81 patients, and root replacement was performed in 63 patients. The first 30 patients of each group were considered to be the surgeons' learning curve. Reoperations were more common in the first 30 patients after subcoronary implantation than after the root replacement. After exclusion of the early reoperations, representing the learning curve, no differences in the severity of aortic regurgitation were observed comparing the subcoronary implantation with the root replacement technique.

Chapter 7 is a description of serial echocardiographic examinations, that were performed in 204 adult patients with a human tissue valve to monitor the process of valve degeneration over time and to assess the influence of determinants on durability. Valves implanted in the subcoronary position showed more initial aortic regurgitation compared to root replacement valves. The severity of aortic regurgitation remained stable during the follow-up for both implantation techniques. An influence of the surgical learning curve on initial aortic regurgitation severity was confirmed in the subcoronary implantation technique. After the learning phase had passed more initial aortic regurgitation after the subcoronary implantation technique persisted.

Chapter 8 contains a general discussion in which the results and conclusions of the studies in Chapters 3 to 7 are described in relation to the objectives of the studies presented in the introduction.

Samenvatting

Aortaklepvervanging door menselijke weefselkleppen is een veelgebruikte therapie bij patiënten met kleplijden. De belangrijkste problemen bij het gebruik van menselijke weefselkleppen zijn het vóórkomen van aortaklepinsufficiëntie en degeneratie, die kunnen leiden tot vroegtijdige reoperatie. Het uitgangspunt van de studie, zoals beschreven in dit proefschrift, is dat met serieel echocardiografisch onderzoek dysfunctie van de donorklep beter en voortijdig te detecteren is dan door de incidentie van reoperatie door klepfalen en klep-gerelateerd overlijden te meten. De invloed van factoren zoals chirurgische implantatietechniek, ontvanger- en donoreigenschappen is tevens onderzocht.

In *hoofdstuk 1* wordt een korte samenvatting gegeven over de geschiedenis van de introductie van menselijke weefselkleppen in de hartchirurgie. Vervolgens worden het me-chanisme van klepfalen, de invloed van bekende risicofactoren en de klinische presentatie van klepfalen besproken. De doelstellingen van dit proefschrift worden beschreven.

In *hoofdstuk 2* wordt de toepassing van echocardiografie bij het vastleggen en graderen van aortaklepinsufficiëntie besproken

Hoofdstuk 3 is een beschrijving van de vergelijking van het meten van aorta-insufficiëntie met kleuren Doppler echocardiografie en cineangiografie. De echocardiografische "jet-breedte" methode heeft een goede correlatie met cineangiografie en maakt een goed onderscheid tussen milde en ernstige aortainsufficiëntie, dit in tegenstelling tot de "jet-oppervlakte" methode.

Hoofdstuk 4 is een beschrijving van de reproduceerbaarheid van de kwantificering van aortaklepinsufficiëntie met de "jet-breedte" en "jet-oppervlakte" methode. De echocardiografische gegevens van 62 patiënten met aortaklepinsufficiëntie werden gebruikt voor het bepalen van de meetvariatie tussen onderzoekers en binnen de individuele onderzoeker. De meetvariatie tussen onderzoekers en binnen de individuele onderzoeker is het kleinst voor de jet-breedte en linker ventrikel uitstroom dimensie, dit in tegenstelling tot de jet-oppervlakte en linker ventrikel oppervlakte metingen. De reproduceerbaarheid van de jet-breedte in relatie tot de linker ventrikel uitstroom in de parasternale lange as is goed.

Hoofdstuk 5 is een beschrijving van specifieke echocardiografische bevindingen die voorkomen na implantatie van de donor weefselklep in aorta positie met de subcoronaire en wortelvervangende techniek. Echovrije ruimten naast de donorklep, zoals pseudoaneurysma en paravalvulaire lekkage, en excentrische jet patronen kwamen frequenter voor na het toepassen van de subcoronaire techniek (41%) dan na de aortawortelvervangende techniek (11%). Deze bevindingen ondersteunen het concept van een beter behoud van klepfunctie indien de donorklep als een functionele eenheid wordt geïmplanteerd.

Hoofdstuk 6 is een beschrijving van de invloed van de chirurgische leerfase op het vóórkomen van vroege reoperaties en de ernst van kleplekkage na het toepassen van de subcoronaire implantatie (n=81) of aortawortelvervangende techniek (n=63). De eerste 30 geopereerde patiënten van beide implantatie technieken werden vergeleken met de later geopereerde patiënten. De incidentie van reoperatie in de eerste 30 geopereerde patiënten met de subcoronaire techniek was hoger in vergelijking met de aortawortelvervangende techniek. Deze vroege reoperatie, als uiting van de chirurgische leerfase, werden in de echocardiografische analyse uitgesloten. In de echocardiografische analyse werd vervolgens geen verschil in ernst van aortainsufficiëntie gevonden tussen de subcoronaire implantatie en de aortawortelvervangende techniek.

Hoofdstuk 7 is een beschrijving van de prospectieve echocardiografische studie die plaatsvond bij 204 patiënten met een menselijke weefselklep in aorta positie. De menselijke weefselkleppen die geïmplanteerd zijn met de subcoronaire techniek toonden meer initiële aortaklepinsufficiëntie dan kleppen geïmplanteerd met de aortawortelvervangende techniek. De invloed van de chirurgische leerfase op de ernst van aortainsufficiëntie, zoals beschreven in hoofdstuk 6, wordt in hoofdstuk 7 bevestigd. Het verschil in ernst van de initiële aortaklepinsufficiëntie bleef bestaan na het passeren van de chirurgische leerfase voor de subcoronaire techniek. De progressie van de ernst van de aortaklepinsufficiëntie was gering en voor beide implantatie technieken gelijk. Er werden geen risicofactoren voor deze geringe progressie aangetoond.

Hoofdstuk 8 is een algemene discussie waarin de belangrijkste resultaten en conclusies van de studies in hoofdstukken 3 tot en met 7 worden besproken, gerelateerd aan de doeleinden zoals gesteld in de inleiding. Enkele overwegingen voor de toekomst worden besproken.

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Curriculum vitae

De auteur van dit proefschrift werd geboren op 7 mei 1966 in Didam. In 1984 behaalde zij het Atheneum diploma aan de Openbare Scholengemeenschap Walburg te Zwijndrecht. In hetzelfde jaar startte zij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens haar studie verrichtte zij onderzoek naar de traditionele geneeskunde in Tamil Nadu, India (Christian Medical College). Haar afstudeeronderzoek richtte zich op de follow-up van kinderen met een middenkwabs-atelectase en vond plaats op de afdeling Kinderpulmonolgie van het Universitair Ziekenhuis Gasthuisberg te Leuven, België (Prof. Dr C. de Boeck). In oktober 1991 behaalde zij het artsexamen. Daarna werkte zij in het Drechtstedenziekenhuis te Zwijndrecht en in het Sint Franciscus Gasthuis te Rotterdam als arts assistent niet in opleiding op de afdeling Cardiologie.

In 1993 begon zij met het in dit proefschrift beschreven onderzoek op de afdeling Thoraxchirurgie (Prof. Dr E. Bos), Erasmus Universiteit Rotterdam. In 1994 werd op het zesde internationale symposium voor Cardiac Bioprotheses te Vancouver, Canada, de "Scientific Committee Award for Investigative Achievement" verkregen voor haar voordracht over de vroege resultaten na humane weefselklep implantatie. Zij werd genomineerd voor de "young investigators award" tijdens de negende jaarlijkse bijeenkomst van de European Association for Cardio-Thoracic Surgery te Parijs in 1995.

In 1996 beeindigde zij haar onderzoek en was zij vervolgens enkele maanden werkzaam als arts-assisent niet in opleiding op de Intensive Care Cardiologie in het Academisch Ziekenhuis Rotterdam.

Sinds oktober 1996 is zij in opleiding tot radioloog in het Academisch Ziekenhuis Groningen (opleider: Dr E.J. van der Jagt).