Changes in the left ventricular outflow tract after transcoronary ablation of septal hypertrophy (TASH) for hypertrophic obstructive cardiomyopathy as assessed by transoesophageal echocardiography and by measuring myocardial glucose utilization and perfusion

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Aims and Methods Transcoronary ablation of septal hypertrophy (TASH) leads to marked clinical and haemodynamic improvement in patients with hypertrophic obstructive cardiomyopathy. In order to obtain more detailed information about changes in the outflow tract after TASH, transoesophageal echocardiography and a repeat invasive investigation were conducted before as well as 2 weeks and 6 months after TASH (n=62). In a subset of patients (n=11), metabolism and perfusion of the myocardium (18F-FDG-PET and 99mTc-MIBI-SPET) were investigated.

Results After TASH there was a typical regional subaortic contraction disorder. It was quantified by a significant decrease in the fractional shortening of the left ventricular end-diastolic diameter, which declined from an average of 40.6% to 18.0%. The end-diastolic diameter increased from an average of 39.1 to 40.6 mm. There was also a significant reduction in septal thickness, which continued for up to 6 months after TASH, from an average of 20.0 mm to 11.1 mm in the region of ablation and from 23.2 to 21.7 mm outside this region. The decrease in the gradient post TASH corresponded with a concomitant significant increase in the outflow tract area from a mean value of 1.04 cm² before the process to a value of 3.0 cm² after. In contrast to coronary heart disease, these changes were accompanied by non-diffuse, well demarcated subaortic-septal necrosis verified by 18F-FDG-PET and 99mTc-MIBI-SPET. On average the TASH induced necrotic area comprised 6.6% of the left ventricle and correlated significantly with echocardiographic changes in the outflow tract.

Conclusions Alterations post TASH indicated that this catheter interventional treatment for hypertrophic obstructive cardiomyopathy affects the specific region of obstruction. The changes reflect a ‘therapeutic remodelling’ of the outflow tract of the left ventricle. They were demonstrable over the entire 6 months investigation period and obviously constituted the basis of post TASH clinical and haemodynamic improvement. Progressive alterations post TASH (post TASH reduction of subaortic septal thickness and an increase in the end-diastolic diameter) need special consideration during long-term follow up.

Key Words: Hypertrophic obstructive cardiomyopathy, catheter therapy, perfusion and glucose metabolism, TASH.
Introduction

In 1991, following studies of chemical ablation of ventricular tachycardia with alcohol in patients with coronary artery disease[1], we commenced basic investigations in patients with hypertrophic obstructive cardiomyopathy (candidates for surgical treatment) with the aim of developing interventional treatment via catheter[2]. This concept was first introduced in 1994[2–5], followed by the first therapeutic application in our hospital in 1995, and its designation, transcoronary ablation of septal hypertrophy[2,3] (TASH). TASH induces a therapeutic septal infarct after selective septal artery injection of alcohol (96% ethanol) and leads to significant clinical and haemodynamic improvement[2,6–14]. It is indicated in severely ill patients with hypertrophic obstructive cardiomyopathy (common subaortic type) refractory to medical treatment and requires a high level of expertise[2,3,6,15].

To investigate changes in the left ventricular outflow tract induced by TASH, transoesophageal multiplane echocardiography was performed together with invasive measurement of the intraventricular gradient in 62 patients. In a subset of 11 patients, 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and 99mTc-methoxyisobutylisonitrile single photon emission tomography (99mTc-MIBI SPET) were performed to determine metabolism and perfusion of the myocardium.

Patients and methods

We started to perform TASH in our hospital in 1995 in severely ill multimorbid patients. The present study comprises all the patients treated successfully so far[6], and for whom the course could be controlled invasively and non-invasively by transoesophageal echocardiography before transcoronary ablation of septal hypertrophy, and 2 weeks and 6 months after the ablation (n=62). All investigations were carried out prospectively. After patient No. 75, we stopped studying the effect of TASH by left heart catheterization 2 weeks after the process. The patients were investigated by means of multiplane transoesophageal echocardiography 2-4 days before TASH as well as about 2 weeks and 6 months after. The patients' age averaged 57.7 ± 13.8 years. Thirty-three were men, 29 were women. All patients had features typical of hypertrophic obstructive cardiomyopathy (Fig. 1)[16,17] with symptoms refractory to medical treatment (NYHA III or IV, or NYHA II with a history of syncope and/or severe angina-like chest pain and/or severe symptoms caused by arrhythmia). The intraventricular gradient was at least 50 mmHg at rest and/or at post-extrasystole.

Transcoronary ablation of septal hypertrophy technique

The TASH technique has been described in detail elsewhere[2,3,5,6] and uses the routinely performed PTCA technique. The gradient was determined by simultaneously measuring the post-stenotic pressure via the guide catheter in the left coronary artery and via a 5 F pigtail catheter placed retrogradely in the pre-stenotic cavity of the left ventricle.

The intraventricular gradient was assessed at rest as well as at post-extrasystole (mean of at least three heart actions). For reproducible conditions the ventricular extrasystole was induced by programmed stimulation of the right ventricle, with a constant coupling interval of about 370 ms.

Figure 1 Transoesophageal echocardiogram in a patient with hypertrophic obstructive (HOCM) and hypertrophic non-obstructive (HNCM) cardiomyopathy. In contrast to HNCM, there is severe narrowing of the outflow tract of the left ventricle caused by a subaortic septal bulge and a systolic anterior movement of the anterior mitral leaflet.
A septal artery suitable for alcohol injection was identified by means of haemodynamic criteria. A significant fall (at least 30%) in the pressure gradient during the primary balloon occlusion and additional augmentation of ischaemia by injection of about 0.5 ml of contrast medium via the balloon catheter was a precondition for subsequent injection of alcohol (Fig. 2). As a rule, primarily the first septal branch of the left anterior descending coronary artery is primarily occluded with a balloon (1.5 mm in diameter and 20 mm long). In the mean 4.3 ± 2.4 ml of 96.0% ethanol were injected. (To date 190 therapeutic procedures have been performed in 165 patients. The amount of alcohol injected has been reduced (e.g. 2.3 ± 1.0 ml of ethanol in the last 50 patients)).

Transoesophageal echocardiography

Multiplane transoesophageal echocardiography was carried out in the supine position in all patients after premedication with 0.3–0.5 mg midazolam and if required 10 mg diazepam i.v. (Hewlett Packard, Sonos 1500 S) using standard projections[18]. However, account was taken of special anatomical conditions in hypertrophic obstructive cardiomyopathy.

In the subaortic cross-sectional image (short axis view), measurements of the end-diastolic and endsystolic diameters, including diastolic septal thickness, were made. The diameters measured were located between the area of ablation of the septum and the free wall, marked by the opening and closing movement of the mitral valve. The end-systolic opening area, assessed by planimetry in the region of obstruction, i.e. at the level of the free edge of the anterior mitral valve, was also measured in a prospective manner in a subset of 34 patients (i.e. from case 28) (Fig. 3). The plane in which the smallest cross section of the obstruction, at the boundary between the septum and the anterior mitral leaflet imaged at end-systole, was chosen (Fig. 3).

To evaluate the acute effect of the alcohol injection, in five patients the subaortic region was imaged and appraised qualitatively by transthoracic echocardiography during the therapeutic session, i.e. immediately before alcohol injection (before and after elimination of the gradient by balloon occlusion and/or additional septal injection of contrast medium) and simultaneously during and immediately after injection of alcohol (Fig. 2).

Creatine phosphokinase activity

The enzyme activity in the serum was determined every hour for 18 h after alcohol injection.

Myocardial perfusion (99mTc-MIBI-SPET) and glucose utilization (18F-FDG-PET)

In 11 patients with a wide range of injected alcohol (6.9 ± 3.7 ml) myocardial perfusion and glucose utilization were investigated by means of 18F-FDG-PET and 99mTc-MIBI-SPET, respectively, on average 88.6 ± 104.2 days after TASH (age 59.1 ± 8.7 years, range 49–74 years, five men, six women). In one patient, these investigations were also carried out 2 days before TASH in addition to the investigation after the procedure.
Resting myocardial perfusion
Resting myocardial perfusion was assessed semiquantitatively by \(^{99m}\text{Tc-MIBI}\) and single photon emission tomography (\(^{99m}\text{Tc-MIBI-SPET}\)). Imaging started 1 h after intravenous resting injection of 740 M Bq \(^{99m}\text{Tc-MIBI}\) using a double headed SPET camera (E.CAM; Siemens Gammasonics Inc., ILL, U.S.A.). Images were acquired with two heads in a 90\(^\circ\) orbit, with a zoom factor of 1-45. Images were reconstructed using filtered back-projection with a Butterworth filter (cut-off 0.6; order 5) and transferred to a SPARCStation 20, running Solaris 2.5 (SUN Microsystems Inc., CA, U.S.A.) for further analysis.

Myocardial glucose utilization
Myocardial glucose utilization was measured by positron emission tomography following intravenous injection of \(^{18}\text{F-FDG}\) using an ECAT EXACT 47 tomograph (Siemens/CTI Inc., TN, U.S.A.) with simultaneous acquisition of 47 cross-sectional images\(^{19}\). An hour before the end of the PET scan, the patient underwent a euglycemic hyperinsulinaemic clamp, achieved by constant infusion of 40 mU insulin \(\cdot m^2\) \(\cdot \) body surface \(\cdot \) min\(^{-1}\), described elsewhere\(^{20-22}\). Plasma glucose levels were measured at 5 min intervals and stabilized by adjusting a glucose infusion system (20% glucose in 500 ml NaCl).

Figure 3
A transoesophageal echocardiogram in a 26-year-old patient with typical subaortic hypertrophic obstructive cardiomyopathy before (upper panel) and after TASH (lower panel). After the ablation there was pronounced widening of the outflow tract (longitudinal view on the left, corresponding to the cross-sectional area on the right).

After positioning the patient on the bed of the PET tomograph, a rectilinear scan was performed using three retractable rod sources, each filled with about 120 M Bq \(^{68}\text{Ge}\). This scan was used to position the left ventricle as close as possible to the centre of the axial and transaxial fields of view of the tomograph. After final positioning, a 20 min transmission scan was performed using the same rod sources. From this scan the attenuation correction coefficients for each line of response in the emission sinograms were calculated. Following the transmission scan, 357 ± 17 M Bq \(^{18}\text{F-FDG}\) were intravenously infused over a 1 min period. A 23 frame dynamic emission scan of 54 min and 30 s duration was used to define the temporal dynamic accumulation of the tracer in the myocardium. This scan consisted of a 30 s background frame, prior to the infusion of \(^{18}\text{F-FDG}\), followed by 12 × 10 s frames, 4 × 30 s frames, 2 × 300 s frames and 4 × 600 s frames. Arterialized venous blood for correction of whole blood/plasma ratios and spill-over was sampled at defined time points (24, 34 and 44 min post injection). Images were reconstructed with a Hanning filter (cut-off 0.5) in a 128 × 128 matrix and transferred to a SPARCStation 20 running Solaris 2.5 (SUN Microsystems Inc., CA, U.S.A.) for further analysis. From the dynamic emission PET scan, parametric images of local myocardial glucose utilization were calculated using the patlak plot, as described elsewhere\(^{23-26}\).

For comparison of local myocardial perfusion and glucose utilization, images of \(^{99m}\text{Tc-MIBI-SPET}\) and \(^{18}\text{F-FDG-PET}\) studies were matched using a dedicated multipurpose imaging tool (MPItool\(^{27,28}\)). Image interpretation was performed visually using quantitative regions of interest. For the latter, an automated contour detection algorithm\(^{29}\), capable of bridging tracer accumulation defects (e.g. myocardial infarction), was used to mark pixels containing left ventricular myocardium in the \(^{99m}\text{Tc-MIBI-SPET}\) and \(^{18}\text{F-FDG-PET}\) studies. Pixels were grouped into a total of 768 (24 planes in 32 regions) regions of interest. In each individual study, local resting myocardial perfusion (PERF loc) and local myocardial glucose utilization (MGU loc) were calculated for each region of interest. PERF loc and MGU loc were expressed as the percentage value of the individual maximum value in each patient study. Mean and standard deviation (SD) of PERF loc and MGU loc in non-infarcted myocardium was calculated by averaging all regions of interest of the anterior, lateral, and inferior myocardial walls in all patients. In each patient, the defect volumes in the \(^{99m}\text{Tc-MIBI-SPET}\) (DV MIBI) and the \(^{18}\text{F-FDG-PET}\) studies (DV FDG) were determined as the total volume of all regions of interest, with PERF loc/ MGU loc < mean - 2*SD.

All patients gave their written consent after it had been explicitly explained that TASH was a new method of treatment.

The statistical calculations were made using the SPSS program, version 7.5. All values are expressed as mean ± SD. Differences were tested by means of the two-tailed Student t-test for paired random samples. A P value <0.05 was regarded as significant. The
Correlation analysis was performed on a bivariate basis with two-tailed tests of significance.

Results

As expected \cite{18,30}, transoesophageal echocardiography generally enabled more precise and more differentiated imaging of the subaortic anatomy of the left ventricle than transthoracic imaging.

Quantitatively, there was a significant decrease in the gradient at rest and after extrasystolic potentiation of the contraction, in the fractional shortening of the end-diastolic diameter and in the septal thickness. Between the second week and the sixth month, the septal thickness was further reduced significantly. The end-diastolic diameter of the left ventricle increased significantly (Fig. 4).

These post TASH alterations were best recognized in the subaortic cross-sectional view and corresponded to a pronounced widening of the outflow tract compared to the pre-TASH findings. Post TASH there was lack of contact between the anterior mitral valve leaflet and the septum and the regional subaortic contraction disorder of the septum (Fig. 3).

The regional contraction disorder observed by transoesophageal echocardiography presented with post TASH hypokinesia and akinesia of the septum and in some cases even with dyskinesia. It corresponded anatomically with the subaortic septal region visualized with contrast medium and observed immediately after induction of ischaemia or after injection of alcohol in the five patients who were investigated during the therapeutic session by transthoracic echocardiography.

Within the disorder of contraction, a post TASH notch-like deformation of the septum was found which resembled conditions following myectomy (Fig. 3) \cite{31}. It was already present 2 weeks after TASH and was strictly localized. In qualitative terms, the cross-section of the disturbed septal contraction was about 30% of the cross-sectional circumference. Septal reduction, from 20.0 mm to 11.1 mm, and the disorder of contraction, expressed by the reduction of fractional shortening from 40.6 to 18.2%, led to an increase in the outflow tract area, from an average of 1.04 m^2 before TASH to 3.0 m^2 after the process (P <0.001).

Investigation of myocardial perfusion, using 99mTc-MIBI-SPET and glucose utilization, using 18F-FDG-PET, showed the following picture. In all patients, a clearly demonstrable myocardial defect was seen post TASH irrespective of the interval to the therapeutic procedure. The post TASH defect was always sharply demarcated. It corresponded anatomically to the regional disorder of contraction in the transoesophageal echocardiography and was matched in terms of perfusion and glucose utilization. The mean defect volume amounted to 10.2 ± 7.8 ml (6.9 ± 3.7% of the entire volume of the left ventricle, 18F-FDG-PET) and 10.7 ± 6.3 ml (6.6 ± 5.9%, 99mTc-MIBI-SPET), respectively. The post TASH peak phosphocreatine kinase activity was 608 ± 391 IU 1^{-1}. 

\begin{table}[h]
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\begin{tabular}{llllllllll}
\hline
\textbf{Gradient (mmHg)} & 54.0 & 6.4 & 6.1 & 142.4 & 29.7 & 30.1 & 6.4 & 6.4 & 6.4 & 40.6 & 40.6 & 18.2 & 18.1 & 18.2 & 18.1 & 20.0 & 13.4 & 11.1^* \\
\textbf{Post-ES grad.} & 41.3 & 15.0 & 8.5 & 49.9 & 34.4 & 38.8 & 6.4 & 6.4 & 6.4 & 8.5 & 8.5 & 11.6 & 12.2 & 12.2 & 12.2 & 2.6 & 3.7 & 3.0 \\
\textbf{EDD (mm)} & 54.0 & 41.3 & 6.4 & 142.4 & 29.7 & 30.1 & 6.4 & 6.4 & 6.4 & 40.6 & 40.6 & 18.2 & 18.1 & 18.2 & 18.1 & 20.0 & 13.4 & 11.1^* \\
\textbf{Septum (mm)} & 20.0 & 2.6 & 3.0 & 20.0 & 2.6 & 3.0 & 20.0 & 2.6 & 3.0 & 20.0 & 2.6 & 3.0 & 20.0 & 2.6 & 3.0 & 20.0 & 2.6 & 3.0 \\
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\end{tabular}
\caption{Gradient, diameter and fractional shortening in the diameter of the left ventricle, and septal thickness before TASH, and 2 weeks and 6 months after TASH (n=62). \textit{Post ES grad.} = post extrasystolic gradient; \textit{EDD} = end-diastolic diameter of the left ventricle; \textit{FS} = fractional shortening of the end-diastolic diameter; \textit{Septum} = septal thickness of the ablated area. *P value <0.001 (septal thickness) for the difference between 2 weeks and 6 months. The septal thickness in the non-ablated area before TASH ( ), 2 weeks ( ) and 6 months ( ) after amounted to 23.2 ± 4.4 mm, 22.0 ± 4.7 mm and 21.7 ± 5.0 mm (P <0.01).}
\end{table}
A slightly pronounced apically situated ‘paradoxical’ defect (i.e. maintained perfusion, but disturbed metabolism) was found, in addition, in three patients, although a disorder of contraction could not be demonstrated in this region.

The correlation between characteristics of the outflow tract revealed numerous significant correlations which were pathophysiologically connected (Table 1) (Figs 5–9).

**Discussion**

The present investigations were carried out in order to obtain more differentiated information on TASH.
induced changes in the outflow tract of the left ventricle.

It was shown that TASH leads to a specifically circumscribed and ongoing subaortic decrease in septal thickness, which could be exactly imaged by means of transoesophageal echocardiography. Similar to the situation after myocardial infarction due to atherosclerosis, this could already be detected at an early stage (2 weeks after TASH). It was also shown that the alcohol injection leads to a pronounced diminished contraction, locally restricted to the subaortic septal site, which corresponds to angiographic findings of the left ventricle.

There was no change in the end-diastolic diameters initially (2 weeks post TASH) followed by a significant increase 6 months later. There was a significant increase in the outflow tract area, from 1.04 cm² to 3.0 cm², resulting from a decrease in septum width and the diminished fractional shortening.

Similar alterations, in the localized contraction disorder and in the diameter, were also described after surgical therapy. A significant increase in the opening area (from 1.1 cm² to 3.8 cm²) was also found postoperatively by means of three dimensional transoesophageal echocardiography.

The post TASH decrease in septal thickness, assessed by the transthoracic echocardiographic approach appeared much less pronounced. Similarly, pronounced septum reduction, detected by transthoracic echocardiography, was reported only in occasional cases, both post TASH and postoperatively, despite a deep myectomy channel in the septum.

Using the transoesophageal approach, the septal thickness in our studies fell appreciably from 20.0 to...
11.1 mm in the region of ablation. Such a decrease post TASH was also observed by use of magnetic resonance tomography[8,40].

The reason for the less pronounced septal reduction, identified by the standard transthoracic echocardiographic approach, may be that this technique only measures the marginal sites of the ablated septal area. In our studies using transoesophageal echocardiography outside the area of ablation the pre TASH septum remained thicker and decreased markedly less post TASH (on average from 23.2 mm to 21.7 mm) as described by other authors using transthoracic echocardiography[7,10,12,30].

The location of the disturbance of the contraction described coincided with the pre TASH maximum of narrowing of outflow tract and corresponded anatomically also to the location of the obstruction found invasively in typical hypertrophic obstructive cardiomyopathy[16,17,41].

Furthermore, the site of the disturbed septal contraction also corresponded with the location of the myocardial defect identified with $^{18}$F-FDG-PET and $^{99m}$Tc-MIBI-SPET, as described for the first time in 1997 in a patient treated by TASH[42]. In conjunction with the increase in peak phosphocreatine kinase activity in the serum the defect originates from alcohol-induced myocardial necrosis. However, this necrosis is entirely different from that seen in coronary artery disease. It is much smaller (on average 6-6% in hypertrophic obstructive cardiomyopathy post TASH and 23%-51% in the left ventricle of the infarct of coronary heart disease)[33,34]. It is sharply demarcated in hypertrophic obstructive cardiomyopathy, whereas in coronary heart disease it is fingerlike and confluent passes into the vital areas of the myocardium. According to histological studies, leucocytic organization and fibrosis, as well as infiltrative myocardial sequestration in terms of removal of necrotic tissue, are absent in the necrosis induced by alcohol even weeks after TASH[6,32]. Using SPET, other authors found a septal perfusion defect after TASH, averaging 9-5% of the left ventricle at a post TASH peak phosphocreatine kinase activity of 1937 IU l $^{-1}$ in the mean[13].

Three of the patients investigated with $^{18}$F-FDG-PET and $^{99m}$Tc-MIBI-SPET showed an unmatched myocardial defect apically, i.e. distal from the actual region of alcohol-induced subaortic necrosis. This myocardial defect was not accompanied by abnormal contraction. It was paradoxical since in contrast to coronary heart disease it involved the metabolism and not the perfusion. This might be explained in that alcohol—which has already been diluted in concentration—passes via collateral vessels between the septal artery selected and the posterior descending artery into the apical capillary terminal vascular bed and only causes partial subsequent myocardial damage. Such collateral connections can be demonstrated relatively frequently in probatory injection of contrast agent into the chosen septal artery (i.e. before alcohol injection)[35]. Focal and partial myocardial lesions, after injection of diluted alcohol into a coronary vessel occluded with a balloon and indeed after injection of contrast medium on its own, have been described histologically in animal experiments[43].

The significant correlations, as listed in Table 1, reflect the relationship of post TASH alterations which can be explained pathophysiologically. Besides volume defect, they comprise reduced subaortic local contraction expressed by a decrease in fractional shortening, a reduction in septal thickness and in the gradient and peak phosphocreatine kinase activity, the amount of alcohol injected and the post TASH increase in the outflow tract area.

The findings indicate a morphological, geometrical and functional remodelling of the outflow tract. They apparently form the basis for the pronounced clinical improvement reported by all groups performing TASH[2,6-14]. This improvement may be caused by the remodelling induced decrease in the gradient both at rest and at exercise[6,44] and by the post TASH reduction or even complete disappearance of mitral incompetence[6]. It should be noted that the mitral valve in typical hypertrophic obstructive cardiomyopathy is always situated in the pre-stenotic area of the left ventricle[16] (Fig. 1).

It is possible that by remodelling the outflow tract the altered autonomic cardiac control in hypertrophic obstructive cardiomyopathy could be improved[45] by reducing hypercontractility and influencing the disturbed sympathetic and parasympathetic cardiac function. Two weeks post TASH, there was a small reduction in septal thickness and a small increase in the end-diastolic diameter (Fig. 4). Further changes cannot be ruled out. This aspect needs special attention at long-term follow-up evaluation. The changes may have originated from the alcohol-specific myocardial necrosis in hypertrophic obstructive cardiomyopathy not organized by connective tissue as usually seen in coronary heart disease[6,32,33,35,43].

Conclusions

The changes show that TASH is apparently a targeted catheter interventional treatment acting on the specific region of obstruction in patients with hypertrophic obstructive cardiomyopathy. The pronounced haemodynamic and clinical post TASH improvement is based on ‘therapeutic remodelling’ of the outflow tract of the left ventricle. It can be demonstrated over the entire 6 months’ investigation period.

References


Changes in LV outflow tract after TASH


