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Prognostische Bedeutung der postinterventionellen Vena contracta Fläche nach Mitraclip-Implantation bei Herzinsuffizienzpatienten mit einer funktionellen Mitralklappeninsuffizienz

Dissertation

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Prognostic implication of post-MitraClip vena contracta area in heart failure patients with functional mitral regurgitation

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KEYWORDS

- heart failure
- MitraClip
- mitral regurgitation
- vena contracta area

Abstract

Aims: Significant functional mitral regurgitation (FMR) in elderly heart failure patients is increasingly being treated by MitraClip implantation. We sought to assess the prognostic implications of the intraprocedural assessment of vena contracta area (VCA) after MitraClip therapy in such patients.

Methods and results: MitraClip therapy with intraprocedural assessment of VCA was performed in 97 heart failure patients (74±10 years; 66 men; left ventricular ejection fraction [LVEF] 31±12%; 93 patients in New York Heart Association [NYHA] functional Class III [n=59] or IV [n=34]; 86 patients with FMR severity 3+ [n=65] or 4+ [n=21]). Ninety-one patients (94%) were discharged with FMR severity ≤2+. During a median follow-up of 13.4 (interquartile range 4.6-21.1) months, 32 patients died. Multivariable Cox regression identified increasing age (HR [95% confidence interval]=1.05 [1.00-1.09], p=0.0395), a glomerular filtration rate <50 ml/min/1.73 m² (HR=2.7 [1.3-5.7], p=0.0115), and post-MitraClip VCA >25 mm² (HR=4.5 [2.1-9.5], p=0.0001) as independent predictors of mortality.

Conclusions: In heart failure patients with FMR undergoing MitraClip therapy, increasing age, impaired baseline renal function and post-MitraClip VCA >25 mm² are strongly associated with mortality. Post-MitraClip VCA may be used as intraprocedural guidance with respect to patients' long-term outcome.

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Abbreviations

FMR functional mitral regurgitation
LVEF left ventricular ejection fraction
MR mitral regurgitation
TOE transoesophageal echocardiography
VCA vena contracta area

Introduction

Functional mitral regurgitation (FMR) due to ischaemic heart disease or dilated cardiomyopathy is common in patients with chronic congestive heart failure[1]. In heart failure patients with a reduced ejection fraction, the presence and severity of FMR is adversely associated with survival[2-5]. Implantation of the MitraClip® (Abbott Vascular, Santa Clara, CA, USA) has become the most frequently used percutaneous modality to treat significant mitral regurgitation in patients not amenable to surgery. According to the 2012 European Society of Cardiology guidelines for valvular heart disease, "... the percutaneous MitraClip procedure may be considered in patients with symptomatic severe FMR despite optimal medical therapy (including cardiac resynchronisation therapy if indicated), who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year..."[6]. Vena contracta area (VCA), measured intraprocedurally by three-dimensional transoesophageal echocardiography (TOE), is a novel variable reflecting the severity of MR: it is directly affected by the intervention and can be determined by the addition of planimetered areas in the presence of multiple regurgitant jets[7-10]. Since about two in three patients undergoing MitraClip therapy in Europe present with FMR and impaired left ventricular function[11], i.e., constitute essentially a heart failure population, we sought to assess the association of post-MitraClip VCA with mortality in this challenging cohort.

Methods

PATIENTS

Of the 192 patients with FMR who underwent MitraClip therapy at our institution between December 2010 and February 2014, only those 97 patients not lost to follow-up in whom VCA was determined before and after the intervention were retrospectively chosen as the study cohort. The mean age of the study patients was 74 years, 68% were men, and all had been adjudicated by Heart Team consensus as inoperable or at high surgical risk **(Table 1)**. Of note, 51% of the patients presented with impaired renal function, as reflected by a glomerular filtration rate <50 ml/min/1.73 m² (estimated via the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), and 84 patients (87%) had impaired left ventricular function with an ejection fraction ≤45%. The vast majority (96%) of the patients were in New York Heart Association (NYHA) functional Class III or IV **(Figure 1)**.

Table 1. Baseline patient characteristics.

N		97
Men, n (%)		66 (68)
Age, years		74±10
Age >75 years, n (%)		52 (54)
Body mass index (BMI), kg/m²		26±5
BMI >25 kg/m², n/N (%)		43/81 (53)
Logistic EuroSCORE, %*		18 [6-36]
Log. EuroSCORE >20%, n/N (%)		48/84 (51)
NT-proBNP, pg/ml*		5,800 [2,697-9,684] (n=53)
CRT, n (%)		27 (28)
ICD therapy, n (%)		22 (23)
LVEDD, mm		64±10
Abnormal LVEDD#, n/N (%)		77/95 (81)
LVESD, mm		53±12
Abnormal LVESD##, n/N (%)		81/93 (87)
LVEDV, ml		177±77
Abnormal LVEDV§, n/N (%)		56/85 (66)
LVESV, ml		177±77
Abnormal LVESV§§, n/N (%)		73/85 (86)
LVEF, %		31±12
LVEF <30%, n (%)		54 (56)
LVEF 30-45%, n (%)		30 (31)
LVEF >45%, n (%)		13 (13)
TAPSE, mm		14.6±4.6
TAPSE <17 mm, n/N (%)		55/83 (66)
NYHA functional class, n (%)	II	4 (4)
	III	59 (61)
	IV	34 (35)
Hypertension, n/N (%)		71/89 (80)
Hyperlipidaemia, n/N (%)		56/91 (62)
Diabetes mellitus, n/N (%)		20/91 (22)
COPD, n/N (%)		24/92 (26)
Pulmonary hypertension¶, n/N (%)		39/95 (59)
Atrial fibrillation, n/N (%)		63/91 (69)
GFR, ml/min/1.73 m²		53±20
GFR <50 ml/min/1.73 m², n (%)		49 (51)
Coronary artery disease, n/N (%)		63/91 (69)
Previous cardiac surgery, n/N (%)		31/91 (34)
Peripheral arterial disease, n/N (%)		16/92 (17)

*Median [IQR]. #>52 mm in women, >58 mm in men; ##>35 mm in women, >40 mm in men [13]. §>106 ml in women, >150 ml in men; §§>42 ml in women, >61 ml in men [13]. ¶Mean pulmonary artery pressure (right heart catheterisation) ≥25 mmHg. COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GFR: glomerular filtration rate; ICD: implantable cardioverter/defibrillator; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end- systolic volume; NYHA: New York Heart Association; TAPSE: tricuspid annular plane systolic excursion

MITRACLIP IMPLANTATION

MitraClip implantations were performed in accordance with a previously described protocol[12]. Procedural success was defined as MR severity ≤2+ at discharge.

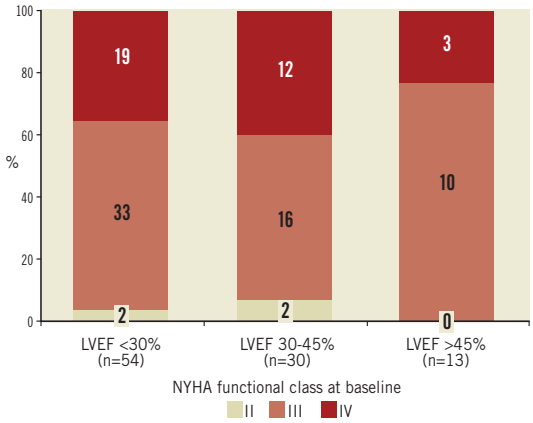

Figure 1. *Distribution of baseline New York Heart Association (NYHA) functional class according to left ventricular ejection fraction (LVEF) category.*

ECHOCARDIOGRAPHY

All patients underwent two-dimensional transthoracic echocardiography (Vivid™ E9; GE Vingmed Ultrasound AS, Horten, Norway, or iE33; Philips Medical Systems, Andover, MA, USA) before and after the intervention. Standard parameters of left ventricular dimension were assessed according to recent guidelines. LVEF was calculated from left ventricular volumes via Simpson's rule, and tricuspid annular plane systolic excursion (TAPSE) served as an assessment of right ventricular function[13,14]. MR severity was graded by way of vena contracta width, effective regurgitant orifice area, and the presence or absence of pulmonary venous flow reversal before MitraClip therapy[15], and via colour flow Doppler jet area after MitraClip therapy[16] **(Online Table 1)**.

Intraprocedural TOE was performed with the iE33 echocardiography system and a corresponding probe (X7-2t). Colour Doppler full volumes of the regurgitant jet were acquired over seven to 10 consecutive cardiac cycles. Nyquist limits were set between 40 and 68 cm/sec; colour gain setting was kept at 50% in all patients. Tissue priority was kept at factory settings. To reduce "stitching" artefacts, patients were put on anaesthesia-controlled breath-hold. In patients with atrial fibrillation, Doppler volumes were acquired during episodes with as little cycle length variation as possible. Care was taken to assess pre- and post-MitraClip MR under similar haemodynamic conditions; when needed, fluid challenges and vasodilators were administered to achieve similar blood pressures.

VCA was assessed as previously described[7-10] using dedicated software (QLAB 8.0; Philips Medical). Before MitraClip therapy, the frame with the largest VCA in early to mid systole (excluding the very first frame) was identified for plane-corrected planimetry[17,18]. In order to assess the cross-sectional area at the neck of the vena contracta precisely, the two orthogonal image planes parallel to the jet direction were manually cropped exactly across the regurgitant jet. The plane perpendicular to the jet direction was then moved along the jet to find the minimum cross-sectional area distal to the regurgitant orifice **(Figure 2)**. After MitraClip implantation, the same approach (i.e., alignment of two orthogonal planes with the regurgitant jet, then finding the smallest cross-sectional area in the third orthogonal plane) was used to measure VCAs for each regurgitant jet; single-jet VCAs were added up to arrive at a final post-MitraClip VCA[10,17]. Very small regurgitant jets with no traceable colour Doppler information at the level of the regurgitant orifice/leaflet tips were not taken into account.

All VCA measurements were performed by two experienced investigators (H. Alessandrini, F. Kreidel). To assess intra-observer variability, both investigators measured post-MitraClip VCAs twice at a three-week interval in 25 randomly selected patients.

FOLLOW-UP

After hospital discharge, follow-up visits were scheduled at six weeks and 12 months, with annual telephone follow-up conducted thereafter.

ETHICS

Written informed consent was obtained from all patients.

STATISTICS

Continuous variables are described as means and standard deviations or as medians plus interquartile range (IQR). Differences between continuous variables were analysed with t-tests (normally distributed data) and the Mann-Whitney U test or Wilcoxon's signed-rank test (non-normally distributed data or markedly unequal group sizes). Three-group comparisons of continuous variables were assessed using one-way analysis of variance. Categorical variables are described with absolute and relative frequencies. Differences between categorical variables were evaluated with the chi-square or Fisher's exact test. Linear regression (Pearson correlation) and Bland-Altman analysis were used to evaluate the relationship and agreement, respectively, between VCA measurements by the two investigators. Intraclass correlation coefficients (ICCs) were calculated to assess the reliability of VCA measurement by the two investigators (two-way mixed model) as well as the reliability of repeated VCA measurement by the same investigator (one-way random model). Patient survival was assessed using the Kaplan-Meier method, log-rank test, and Cox proportional hazards regression analysis. All covariates which were statistically significant ($p<0.05$) on univariate analysis were entered into a "full" multivariable proportional hazards model that adhered to the "10 events per independent variable" recommendation[19].

A two-tailed p-value <0.05 was considered statistically significant, except for multiple (n=3) two-group comparisons, for which $p<0.0167$ was considered statistically significant. Statistical analyses utilised the StatView 4.5 (Abacus Concepts, Inc., Berkeley, CA, USA) and SPSS, Version 22 (IBM Corp., Armonk, NY, USA) software packages.

Results

PROCEDURAL OUTCOMES

In the course of the 97 interventions, a total of 149 clips were implanted, with 51 patients receiving a single clip, 41 patients

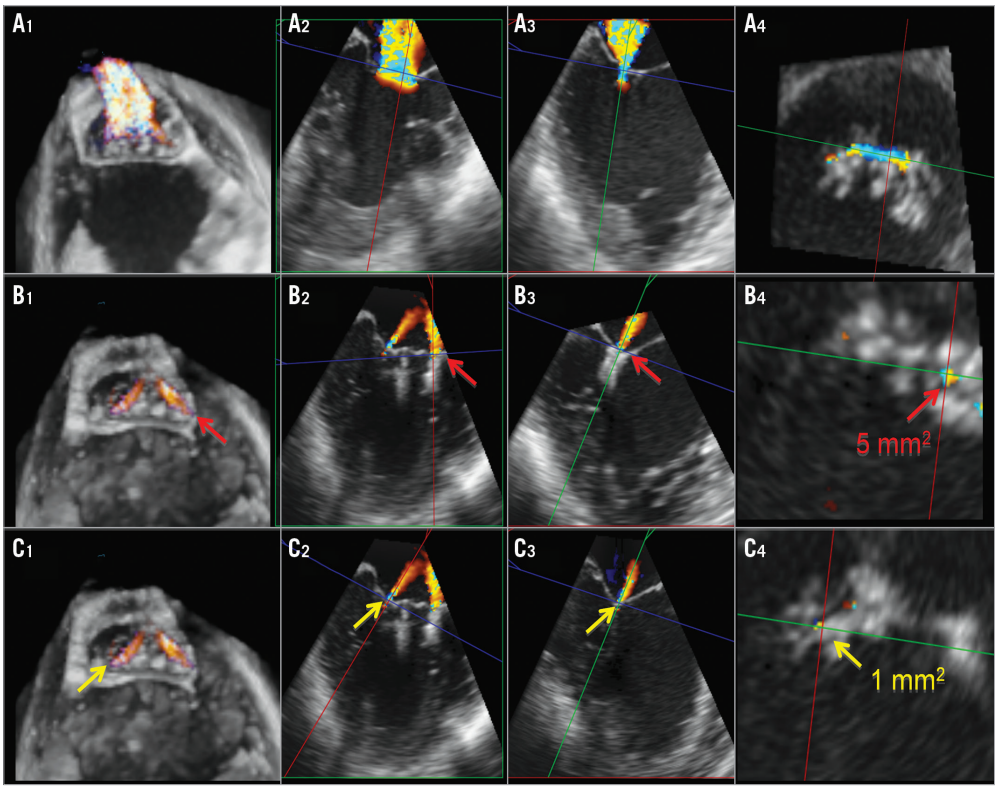

Figure 2. *Measurement of VCA by 3D TOE before and after MitraClip implantation. A1-A4 illustrate findings before MitraClip implantation. A1: full-volume colour Doppler view of grade 3+ MR. A2: view of regurgitant jet in cut plane aligned with the jet; red and blue lines denote cut planes orthogonal to the one shown. A3: view of regurgitant jet in cut plane denoted by red line in panel A2; green line denotes cut plane shown in panel A2. A4: view of VCA in cut plane shown in panels A2 and A3 as blue line; VCA was 45 mm². B1-B4 and C1-C4 illustrate corresponding findings for lateral (red arrows) and medial regurgitant jet (yellow arrows), respectively, persisting after MitraClip implantation. With lateral jet VCA 5 mm² and medial jet VCA 1 mm², total post-MitraClip VCA was 6 mm².*

receiving two clips, and five patients receiving three (n=4) or four (n=1) clips. The mean number of regurgitant jets visualised on transthoracic echocardiography in the apical two-chamber view was 1.2±0.6 (range 0-3). Median total device time, i.e., the time from transseptal puncture to withdrawal of the clip delivery system from the left atrium, was 53 (IQR 36-88) minutes. With baseline MR severity predominantly 3+ (n=42) or 4+ (n=41), the interventions resulted in patients being discharged mostly with MR 1+ (n=52) or 2+ (n=39) **(Figure 3)**. Procedural failures were encountered in six patients (6.2%).

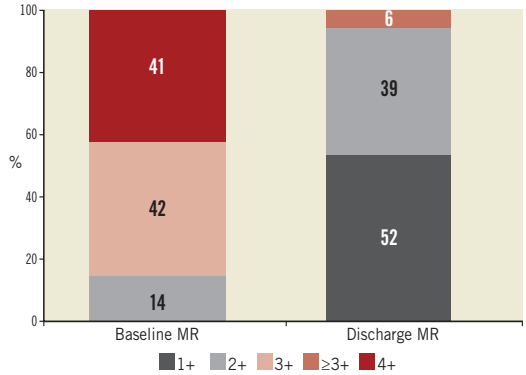

Figure 3. *Distribution of mitral regurgitation (MR) severity at baseline and discharge in the 97 study patients.*

VCA MEASUREMENT

With VCA values ranging between 0 and 70 mm², the mean difference between two measurements was 0.6±2.8 mm² (ICC=0.986; 95% confidence interval [CI]: 0.969 to 0.994, p<0.0001) for one investigator and 3.2±4.5 mm² (ICC=0.817; 95% CI: 0.631 to 0.915, p<0.0001) for the other. Inter-observer variability for all 194 (97 pre- and 97 post-MitraClip) VCA measurements is illustrated in **Figure 4.** Overall correlation between investigators was good (Pearson's r=0.95, p<0.001; ICC=0.949; 95% CI: 0.933 to 0.961, p<0.0001). The Bland-Altman plot revealed a mean bias close to 0 mm² (+1 mm² for pre-, –1 mm² for post-MitraClip VCA measurements), with markedly lower 95% limits of agreement (–23.5 mm² to 21.5 mm²) for post-MitraClip measurements.

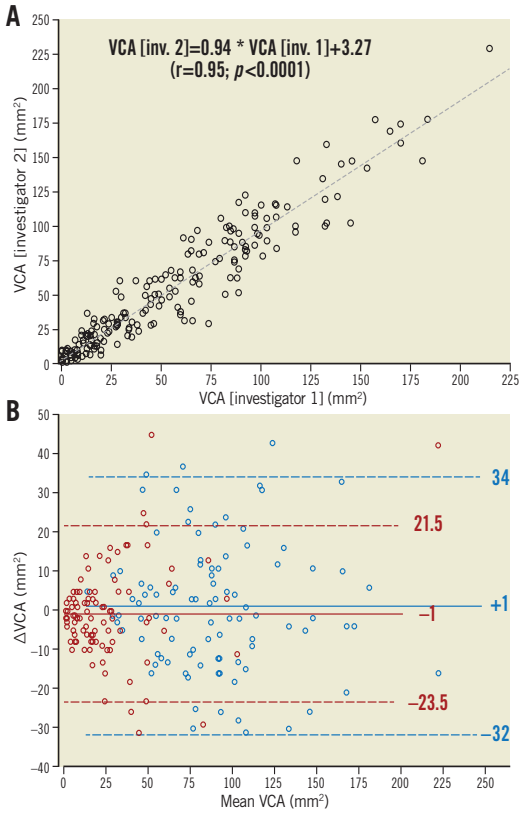

Figure 4. *Statistical evaluation of VCA measurements. A) Correlation of VCA measurements by two investigators. Pearson's correlation coefficient is 0.95. B) Bland-Altman plot of pre- (blue circles) and post-MitraClip (red circles) VCA measurements in 97 patients. Solid horizontal lines denote the mean difference in VCA measurements between the two investigators: +1 mm² for pre-MC, -1 mm² for post-MC measurements. Broken horizontal lines mark the upper and lower 95% limits of agreement (±1.96 standard deviations). MC: MitraClip*

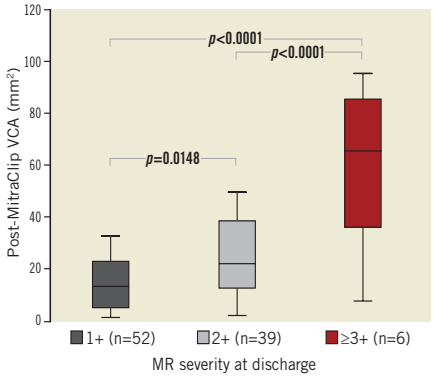

Figure 5. *Box plots of post-MitraClip VCA according to MR severity at discharge.*

The mean VCA between the two investigators was used for all subsequent analyses.

MitraClip implantation resulted in a significant decrease in VCA from 86 (median; IQR 60-108) mm² pre-MitraClip to 17 (7-29) mm² at the end of the procedure (post-MitraClip; p<0.0001). Post-MitraClip VCA increased with increasing discharge MR grade; however, there was pronounced overlap of VCA values between MR grades **(Figure 5)**.

FOLLOW-UP

With two patients lost to follow-up, 95 patients were followed for a median of 13.4 (IQR 4.6-21.1) months. During follow-up, a total of 32 patients died at a median of 408 (IQR 141-642) days post-MitraClip (29 [33%] of 89 successfully, three of six unsuccessfully treated patients). The cause of death could not be determined in four patients; 24 patients died of cardiac reasons at a median of 130 (50-360) days, and the other four patients died of non-cardiac reasons at a median of 57 (26-292) days (p=0.32). Latest post-MitraClip functional status was assessed in 43 of the 63 surviving, successfully treated patients at a median of 18 (14-27) months. At that time, 28 patients (65%) were in NYHA functional Class I or II, with improvement in NYHA class noted in 31 patients (72%), no change in 10 patients (23%), and worsening in two (5%).

To assess predictors of mortality, pertinent procedural, clinical and echocardiographic variables were tested in univariate Cox proportional hazards models. Increasing age, a logistic EuroSCORE >20%, impaired renal function at baseline, the presence of peripheral arterial disease, and a post-MitraClip VCA >25 mm² turned out to be predictive of mortality. Notably, impaired LVEF (≤45%), NYHA functional Class IV and discharge MR severity did not impact on mortality **(Table 2)**. With no apparent differential impact of the lower two post-MitraClip VCA terciles on mortality (hazard ratio [HR] 0.9, p=0.88), and since the logistic EuroSCORE incorporates age, post-MitraClip VCA dichotomised at 25 mm², age, impaired baseline renal function and peripheral arterial disease were tested in a multivariable proportional hazards model. Increasing age, post-MitraClip VCA >25 mm² and impaired renal function prevailed as statistically significant, independent predictors of mortality, with HRs of 1.05 (p=0.0395), 4.5 (p=0.0001) and 2.7 (p=0.0115), respectively **(Table 2)**.

To illustrate the association of post-MitraClip VCA with survival, **Figure 6** shows a statistically significant difference (p=0.0005) between survival curves according to terciles of post-MitraClip VCA. *Post hoc* two-group comparisons revealed no difference in survival between patients in the lower vs. the middle post-MitraClip VCA tercile (<10 mm² vs. 10-25 mm², p=0.83), but statistically significant differences in survival between patients in the middle vs. the upper tercile (10-25 mm² vs. >25 mm², p=0.0015), and between patients in the lower vs. the upper tercile (<10 mm² vs. >25 mm², p=0.0028). Survival estimates are given in **Online Table 2**.

Table 2. Predictors of mortality.

	Univariate analysis		Multivariable* analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Procedural				
Procedural failure	1.7 (0.5-5.6)	0.39		
Clinical				
Female gender	0.7 (0.3-1.5)	0.37		
Age, years	1.05 (1.00-1.09)	0.0344	1.05 (1.00-1.09)	0.0395
BMI >25 kg/m²	0.7 (0.4-1.4)	0.34		
Logistic EuroSCORE >20%	2.22 (1.1-4.7)	0.0340		
Hypertension	0.7 (0.3-1.5)	0.35		
Hyperlipidaemia	0.9 (0.5-1.9)	0.84		
Diabetes	1.2 (0.5-2.6)	0.70		
COPD	1.6 (0.8-3.5)	0.20		
Pulmonary hypertension¶	1.6 (0.8-3.2)	0.22		
Atrial fibrillation	1.1 (0.4-2.0)	0.82		
Impaired renal function‡	2.4 (1.2-4.9)	0.0197	2.7 (1.3-5.7)	0.0115
Coronary artery disease	1.2 (0.6-2.8)	0.61		
Previous cardiac surgery	1.7 (0.9-3.4)	0.13		
Peripheral arterial disease	2.2 (1.0-4.8)	0.0447	1.9 (0.8-4.3)	0.12
CRT	0.7 (0.3-1.5)	0.34		
NYHA IV (vs. II/III)	1.6 (0.8-3.3)	0.16		
Echocardiographic				
Abnormal LVEDD#	0.9 (0.4-2.1)	0.77		
Abnormal LVESD##	1.2 (0.4-3.4)	0.76		
Abnormal LVEDV§	0.8 (0.4-1.6)	0.45		
Abnormal LVESV§§	1.1 (0.4-3.2)	0.87		
LVEF <30% (vs. >45%)	1.1 (0.4-2.9)	0.93		
LVEF 30-45% (vs. >45%)	0.8 (0.3-2.4)	0.66		
Pre-MC TAPSE <17 mm	2.4 (1.0-5.9)	0.06		
Discharge MR 1+/2+ (vs. 3+)	0.6 (0.2-2.0)	0.39		
Discharge MR 2+ (vs. 1+)	1.0 (0.5-2.2)	0.95		
Pre-MC VCA ≥86 mm²	0.8 (0.4-1.7)	0.61		
Post-MC VCA				
>25 mm² vs. ≤10 mm²	3.6 (1.5-9.1)	0.0055		
10-25 mm² vs. ≤10 mm²	0.9 (0.3-2.9)	0.88		
>25 mm² vs. ≤25 mm²	3.8 (1.9-7.8)	0.0003	4.5 (2.1-9.5)	0.0001

*Full model of covariates found statistically significant on univariate analysis. Logistic EuroSCORE not included as it includes age. #>52 mm in women, >58 mm in men; ##>35 mm in women, >40 mm in men[13]. §>106 ml in women, >150 ml in men; §§>42 ml in women, >61 ml in men[13]. ‡ Glomerular filtration rate (CKD-EPI formula) <50 ml/min/1.73 m². ¶ Mean pulmonary artery pressure (right heart catheterisation) ≥25 mmHg. CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; HR: hazard ratio; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; MC: MitraClip; MR: mitral regurgitation; PAP: pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion

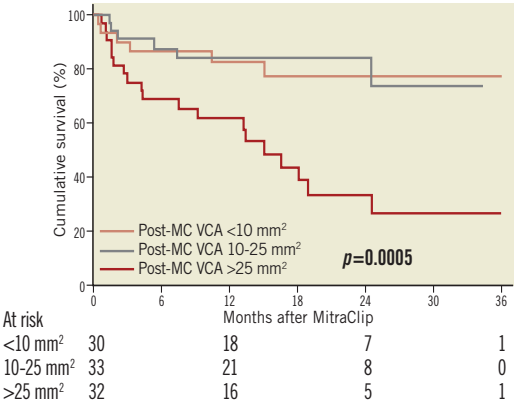

Figure 6. *Cumulative survival curves in 95 patients according to terciles of post-MitraClip VCA. Log-rank p=0.0005 indicates overall difference between survival curves. MC: MitraClip*

Discussion

MAJOR FINDINGS

Unique to this single-centre study of 97 heart failure patients with predominantly moderate-to-severe (3+) or severe (4+) FMR is the finding of a strong association of mortality with post-MitraClip VCA. Compared with patients in whom VCA was ≤25 mm² after MitraClip implantation, the likelihood of death during follow-up was increased by a factor of 4.5 in patients with a post-MitraClip VCA >25 mm². The only other covariates independently and strongly predictive of mortality were increasing age and impaired baseline renal function, defined as a glomerular filtration rate <50 ml/min/1.73 m².

Functional assessment in 43 of our patients at a median of 18 months after successful MitraClip implantation revealed that 72% had improved from baseline, such that roughly two thirds were in NYHA functional Class I or II at that time point.

The primary intention of our study was to assess whether three-dimensional VCA as a fairly easily acquired parameter is of prognostic value. A previous study found that a reduction in VCA by >50% was associated with a smaller annulus area pre-MitraClip and a greater reduction in atrial and ventricular volumes six months post-MitraClip[17], but, to the best of our knowledge, a VCA of 25 mm² has never been discussed as a marker of procedural success.

PREDICTORS OF MORTALITY AFTER MITRACLIP THERAPY

Of note, in our study, baseline LVEF and baseline NYHA functional class were not associated with mortality after MitraClip therapy. These covariates were found to predict mortality in the German TRAMI (n=749) and the Italian GRASP-IT (n=304) registries[20,21]. However, it must be realised that almost all of our patients had impaired left ventricular function (mean LVEF 31%, n=84 with LVEF ≤45%) and that almost all presented with heart failure symptoms of NYHA functional Class III or IV. Apparently, in this patient cohort, minor variations in LVEF towards the better or the worse did not affect mortality. NYHA functional Class III at the time of the intervention, as opposed to NYHA Class IV, appeared to be beneficial in terms of survival only for the first year after treatment and thus corresponds to the finding of Franzen and co-workers[22]. By two years, however, that benefit was lost in our patients.

Both the TRAMI and GRASP-IT registries identified procedural failure as predictive of mortality[20,21]. With a procedural failure rate of only 6.2% in the 97 patients of our study, an association between procedural outcome and mortality was not apparent.

CLINICAL RELEVANCE

The presence of MR in heart failure patients has been shown to impact adversely on the patients' prognosis: in particular, mortality was directly associated with the severity of MR[2-5]. In our study, however, we did not observe an association with mortality of discharge MR severity assessed by regurgitant colour flow jet area. Apparently, post-MitraClip MR grade as determined via that variable is not a reliable representation of the true severity of residual MR.

Since VCA can be measured during the procedure, post-MitraClip VCA assessment may become a means to indicate whether the number of clips implanted is sufficient in terms of prognosis or not. In our patients, a post-MitraClip VCA >25 mm² was associated with a poor prognosis. Although it is tempting to consider a post-MitraClip VCA of 25 mm² as a cut-off that discriminates patients with a favourable prognosis from those with a poor prognosis, it must be realised that grouping of patients by terciles is arbitrary. The 25 mm² value represents the upper limit of the middle tercile (i.e., the 67th percentile of the total post-MitraClip VCA distribution) in our cohort of 97 patients; the uncertainty when considering 25 mm² as a generally valid cut-off is reflected by a 95% confidence interval ranging from 21 to 30 mm². Therefore, greater numbers of patients are needed to confirm the clinical validity of the 25 mm² post-MitraClip VCA cut-off.

Limitations

Patients in this retrospective single-centre study were not enrolled consecutively but rather based on the availability of i) VCA measurements pre and post MitraClip therapy, and ii) follow-up information. The study did not involve an independent echocardiographic core laboratory. The presence or absence of reverse remodelling and its prognostic impact were not assessed, and the velocity time integral across the mitral valve was not measured; therefore, regurgitant volumes could not be calculated retrospectively. The number of patients studied was not high enough for a narrow 95% confidence interval associated with the 25 mm² post-MitraClip VCA cut-off. Validation of a prognostically relevant cut-off would require a separate patient population.

Conclusions

In heart failure patients undergoing MitraClip therapy for significant functional MR, we have introduced the "new" quantitative echocardiographic variable of post-MitraClip VCA to assess prognosis. Post-MitraClip VCA may lend itself as a tool to guide interventional decision making with respect to the patient's long-term outcome. Our findings require prospective validation in larger patient cohorts.

Impact on daily practice

Intraprocedural measurement of VCA by 3D TOE may be helpful to assess the acute outcome of MitraClip implantation.

Conflict of interest statement

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Supplementary data

Online Table 1. Grading of functional MR severity by transthoracic echocardiography before and after MitraClip therapy.

Online Table 2. Kaplan-Meier estimates of survival.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/113th_issue/318

Supplementary data

Online Table 1. Grading of functional MR severity by transthoracic echocardiography before and after MitraClip therapy.

Before MitraClip therapy		
2+	**3+**	**4+**
VC width <7 mm AND EROA <20 mm²	(VC width ≥7 mm OR EROA ≥20 mm²); NO Systolic PV flow reversal	(VC width ≥7 mm OR EROA ≥20 mm²) AND Systolic PV flow reversal
EROA determined via proximal isovelocity surface area (PISA) method; VC width measured in apical 3-chamber view.		
After MitraClip therapy		
2+	**3+**	**4+**
CFD jet area <4 cm²	CFD jet area 4-6 cm²	CFD jet area >6 cm²
CFD jet areas assessed in apical 2-chamber view and summed in cases of multiple jets.		
CFD: colour flow Doppler; EROA: effective regurgitant orifice area; PV: pulmonary vein; VC: vena contracta		

Online Table 2. Kaplan-Meier estimates of survival.

	30 days (%)	6 months (%)	1 year (%)	2 years (%)
All patients (n=95 initially at risk)	96.8 [93.3-100]	80.8 [72.9-88.8]	75.9 [67.0-84.7]	63.1 [51.7-74.6]
Patients with post-MC VCA <10 mm² (n=30 initially at risk)	93.3 [84.4-100]	86.5 [74.3-98.8]	82.4 [68.3-96.5]	76.9 [60.1-93.7]
Patients with post-MC VCA 10-25 mm² (n=33 initially at risk)	100 [100-100]	87.4 [75.8-99.0]	83.9 [70.9-96.9]	83.9 [70.9-96.9]
Patients with post-MC VCA >25 mm² (n=32 initially at risk)	96.8 [85.4-100]	68.8 [52.7-84.8]	61.9 [44.8-78.9]	33.1 [13.7-52.5]
[ ]: 95% confidence interval. MC: MitraClip				

2. Darstellung der Publikation

2.1 Einleitung

Die Mitralklappeninsuffizienz (MI) ist nach der Aortenklappenstenose die zweithäufigste Klappenerkrankung bei Erwachsenen (1). Sie wird gemäß der Ätiologie in organische (primäre) und funktionelle (sekundäre) Insuffizienzen unterteilt. Die funktionelle Mitralinsuffizienz (FMR) ist bei Patienten mit ischämischer oder dilatativer Kardiomyopathie durch eine Dilatation des Klappenringes oder einer Zügelung eines bzw. beider Segel infolge Veränderung der Ventrikelgeometrie bedingt (2). Die Prognose von Patienten mit Herzinsuffizienz und eingeschränkter systolischer linksventrikulärer Funktion und zusätzlicher höhergradiger FMR ist signifikant schlechter im Vergleich zu Patienten ohne oder mit nur leichter Insuffizienz (3,4). Die perkutane Therapie mittels Mitraclip – Device (MCD) wird seit 2008 in zunehmendem Maße eingesetzt und bietet eine effektive und sichere Option zur Behandlung von Herzinsuffizienzpatienten mit einer relevanten FMR (5).

Die 3D-Vena contracta Fläche (3D-VCA) ist ein relativ neuer Parameter, um die Mitralklappeninsuffizienz zu graduieren (6,7). Die Bestimmung erfolgt über die 3D-transösophageale Echokardiographie (3D-TEE) mittels planimetrischer Analyse der auf Koaptationsebene erhobenen Farbjetquerschnittsfläche. Der Vorteil dieser Methode ist, dass damit multiple Regurgitationsjets analysiert und aus deren Flächensumme ein Gesamtwert bestimmt werden kann (8,9).

Das Ziel der Untersuchung ist die prognostische Evaluierung der 3D-VCA nach Behandlung einer höhergradigen Mitralinsuffizienz mittels MCD bei symptomatischen Herzinsuffizienzpatienten.

2.2 Material und Methoden

Im Behandlungszeitraum zwischen Dezember 2010 bis Februar 2014 wurden an unserem Zentrum insgesamt 192 Patienten mit einer FMR mittels MCD behandelt. Alle Patienten waren zuvor durch die Konsensentscheidung des klinikinternen Heartteams als inoperabel oder Hochrisikopatient eingestuft worden. In die Studie konnten letztlich 97 Patienten eingeschlossen werden, bei denen retrospektiv, sowohl echokardiographisch die transösophageale 3D-VCA prä- und postinterventionell analysiert werden konnte, als auch eine klinische Nachbeobachtung vorhanden war. Das Folluw up erfolgte im Rahmen der 6-wöchigen und 12-monatigen Nachsorgekontrollen, im weiteren Verlauf wurden telefonische Follow up Kontrollen durchgeführt.

Insgesamt wiesen 84/97 (87%) Patienten eine eingeschränkte linksventrikuläre Funktion (EF ≤ 45%) auf und 49/97 (51%) Patienten hatten eine eingeschränkte Nierenfunktion (GFR < 50 ml/min/1,73 m²). Weitere 93/97 (96%) Patienten befanden sich zum Zeitpunkt der Klappenintervention im NYHA-Stadium 3 und 4.

Alle Patienten wurden mittels transthorakaler Echokardiographie prä- und postinterventionell untersucht. Standartparameter wie die LV-Funktion sowie Dimensionen wurden gemäß der aktuellen echokardiographischen Guidelines abgeleitet (10). Die Graduierung der Mitralinsuffizienz vor und nach der Intervention erfolgte über ein multimodales Vorgehen bestehend aus Breite der Vena contracta, der effektiven Regurgitationsfläche (EROA), dem Vorliegen eines retrograden Pulmonalvenenflusses (19), sowie ergänzend über die Farbdopplerfläche (11). Diese Vorgehensweise entspricht auch den EVEREST-Graduierungskriterien nach MC-Intervention durch Foster und Mitarbeiter (11).

Die Objektivierung der transösophageal bestimmten 3D-VCA jeweils vor und nach der MC-Intervention erfolgte durch Generierung eines 3D-Farbvolumens und anschließender Off Line-Analyse über die QLAB-Software (Philips Medical). Hiernach wurde mittels dreier orthogonaler Querschnittsebenen die schmalste Stelle der Gesamtquerschnittsfläche im Rahmen der Frühsystole objektiviert. Bei multiplen Insuffizienzjets wurden diese jeweils einzeln planimetrisch analysiert und die Gesamtsumme zu einer gesamt 3D VCA summiert (siehe Abbildung 2 in der Publikation).

2.3 Ergebnisse

Insgesamt wurden 141 MCD implantiert, wobei bei 51/97 (53 %) Patienten eine 1-Clip Therapie, bei 41 (42 %) Patienten eine 2-Clip, bei 4 Patienten (4 %) eine 3-Clip und bei 1 Patient (1 %) eine 4-Clip Strategie erfolgte. Bei Entlassung hatten 91/97 (94 %) Patienten eine Mitralinsuffizienz Grad ≤ 2. Die pVCA Messungen der 97 Patienten (von 2 echokardiographisch erfahrenen Ärzten durchgeführt) flossen dann als mean-Werte aus den beiden Messreihen in die statistische Analyse ein. Die Ergebnisse inklusive der Intra- und Interraterreliabilität zwischen den beiden Messreihen wurden in der Publikation ausführlich dargestellt. Zwei der 97 Patienten gingen im Follow up verloren, so dass die Daten von 95 Patienten in der Überlebenskurve abgebildet wurden.
Letztlich kann aus den Ergebnissen der Prädiktorenanalyse folgendes abgeleitet werden:

1. In der univariaten Regressionsanalyse hinsichtlich Outcome zeigten sich die Baselineprädiktoren Alter, periphere arterielle Verschlusskrankheit (pAVK), Niereninsuffizienz, logistische Euroscore > 20 signifikant ($p<0.05$) und von den echokardiographischen Prädiktoren die Größe der postinterventionell gemessenen VCA (pVCA) hochsignifikant ($p<0.001$).
2. In der multivariaten Analyse zeigten das Alter einen signifikanten ($p<0.05$), die Niereninsuffizienz und die pVCA einen hochsignifikanten Einfluss auf das Outcome.
3. Patienten mit einer pVCA ≥ 25 mm² zeigten in unserem Studienkollektiv prognostisch ein deutlich schlechteres Outcome im Vergleich zu Patienten mit einer pVCA < 25 mm².

2.4 Diskussion

Das Ziel der Studie war bekannte Baseline- sowie echokardiographische Prädiktoren hinsichtlich Outcome bei Patienten mit systolischer Herzinsuffizienz und funktioneller Mitralinsuffizienz zu untersuchen. Die Ergebnisse ergaben, dass neben wissenschaftlich bereits anerkannten Prädiktoren wie Alter und Niereninsuffizienz auch die Größe der postinterventionell gemessenen VCA (pVCA) einen hochsignifikanten Einfluss auf das Outcome von MCD behandelten Patienten hat. Besonders ab einem kumulativen Wert der pVCA über 25 mm² zeigen Patienten eine signifikant erhöhte Sterblichkeit. Einschränkend muss hierbei festgestellt werden, dass es sich dabei nicht um einen Cut off Wert handelt. Der Wert spiegelt den Patientenanteil wieder, deren pVCA-Wert im oberen Drittelbereich der Verteilung in unserem retrospektiv untersuchten Kollektiv lag.

Vorhergehende Studien konnten auch die hochgradig eingeschränkte linksventrikuläre Funktion, die NYHA Klasse und den Grad der residuellen Mitralinsuffizienz (5, 12,13,14) als weitere Prädiktoren identifizieren. Die pVCA wurde bis zum Zeitpunkt der Publikation nicht als Outcomeprädiktor untersucht. Anders als die 2D-VCA, bei der die Summation der Vena contracta-Breite bei multiplen Regurgitationsjets zu einer Überschätzung der Mitralinsuffizienz führen kann (15), bietet die 3D-VCA diverse Vorteile. In erster Linie kann sie nach oder während der MC-Intervention bestimmt werden und bietet somit die Möglichkeit unmittelbar nach Einsetzen des MCD auf eine Reduktion der Regurgitationsfläche als Erfolgsindikator hinzuweisen. Des Weiteren können neben der einfachen Summation der Regurgitationsflächen (8) auch exzentrisch gerichtete Jets evaluiert und somit besser graduiert werden (6). Abschließend wurde die direkte planimetrische Bestimmung der 3D VCA bereits als valide Methodik von Shanks bzw. Marsan und Mitarbeiter beschrieben. Hierbei konnte eine signifikant höhere Korrelation zwischen echokardiographisch bestimmter 3D-VCA und 2D-VCA im Vergleich mit der 3D-VCA der Magentresonanztomographie festgestellt werden (16,17).

In diversen Studien konnte der starke prognostische Einfluss der residuellen Mitralinsuffizienz nach MC-Intervention auf das Überleben nachgewiesen werden. In unserer Studie konnten wir diesen Einfluss nicht nachweisen. Es muss jedoch eingeräumt werden, dass die Bestimmung der residuellen Mitralinsuffizienz in unserem Echolabor lediglich über die Größe der Jetfläche im transthorakalen 2- Kammerblick erfolgte. Die Graduierung der Mitralinsuffizienz vor und nach der MC-Intervention kann

unter anderem durch Anwendung der EVEREST-Graduierungskriterien nach Foster und Mitarbeitern (11) erfolgen. Als Einschränkung in unserer Studie muss festgehalten werden, dass aufgrund des inkompletten echokardiographischen Datensatzes bestimmter Parameter diese Option nicht zu Verfügung stand und lediglich die Summe der transthorakalen planimetrisch bestimmten 2D-Regurgitationsjetfläche(n) als Graduierungskriterium nach MC-Intervention verwendet werden konnte.

Als weiterer prognostischer Outcomeparameter nach MC konnte in den beiden Registerstudien TRAMI sowie GRASP-IT mit zusammen über 1000 Patienten der periprozedurale Erfolg der Klappenintervention objektiviert werden (12,18). In unserer Studie konnten wir diesen Einfluss nicht bestätigen, möglicherweise bedingt durch die zu geringe Anzahl an Patienten.

Als Limitation der Studie muss erwähnt werden, dass die Patienten nicht konsekutiv eingeschlossen wurden. Dies ist darauf zurückzuführen, dass die Ermittlung der prä- und postinterventionellen 3D VCA nicht bei allen Patienten erfolgte. Des Weiteren wurden die echokardiographischen Parameter nicht von einem externen Echolabor gegengeprüft. Der prognostische Einfluss eines eventuell vorhandenen linksventrikulären Remodellings als Verlaufsparameter wurde nicht berücksichtigt. Die Gesamtanzahl der Patienten war zu niedrig, um daraus einen pVCA cut-off Wert zu berechnen.

Zusammengefasst kann aus der Studie abgeleitet werden, dass die intraprozedurale echokardiographische Ermittlung der 3D VCA einerseits die Entscheidung erleichtern kann, ob gegebenenfalls ein zusätzliches MCD implantiert werden soll. Zum anderen stellt die pVCA, neben dem Alter und der Niereninsuffizienz einen starken Outcomeprädiktor bei Patienten mit funktioneller Mitralklappeninsuffizienz dar.

2.5 Zusammenfassung

Die perkutane Mitralklappentherapie mittels Mitraclipdevice stellt eine sichere und effektive Behandlungsmodalität bei Patienten mit funktioneller Mitralinsuffizienz dar und hat das Spektrum der Therapieoptionen entscheidend verändert. Die Objektivierung prä-und postinterventioneller Prädiktoren kann die Identifikation geeigneter Patienten erleichtern und das Outcome entsprechend verbessern. Das Ziel der retrospektiven Studie war es, klinische und echokardiographische Prädiktoren vor und perinterventionell bzw. nach MC-Intervention zu identifizieren, welche einen Einfluss auf das Outcome haben.

Bei insgesamt 97 Patienten konnten das Alter als unabhängiger signifikanter Outcomeprädiktor ($p<0.05$), die Niereninsuffizienz und die postinterventionelle 3D-VCA (pVCA) als hochsignifikante ($p<0.001$) unabhängige Outcomeprädiktoren objektiviert werden. Im Weiteren zeigten Patienten ab einer pVCA $\geq$ 25 mm² ein deutlich schlechteres Outcome im Vergleich zu Patienten mit einer pVCA < 25 mm².

Schlussfolgernd kann festgehalten werden, dass durch die Bestimmung der pVCA bereits im Hybridlabor ein potentieller Outcomeprädiktor zur Verfügung steht. Aus diesem Grund kann durch die Erhebung der pVCA bereits frühzeitig die Entscheidung zur Implantation eines zusätzlichen MCD erleichtert werden.

2.6 Abstract

The percutaneous mitral-valve-therapy via the mitral-clip device constitutes a safe and effective modality of treatment for patients with mitral valve insufficiency and has significantly broadened the spectrum of treatment options. By objectifying pre- and post-interventional predictors, the identification of suitable patients is facilitated, and the outcome improved. The aim of the retrospective study was to identify clinical and echocardiographic predictors, pre-and peri-interventional or rather, after MC-intervention, which have a significant effect on the outcome.

Significant outcome predictors could be identified in 97 patients, with age being objectified as an independent outcome predictor ($p<0.05$), renal insufficiency and post-interventional 3D-VCA (pVCA) as highly significant ($p<0.001$) independent outcome predictors. Moreover, patients around a pVCA ≥ 25 mm² showed a substantially poorer outcome compared to patients with a pVCA< 25 mm². Conclusively it can be said that by determining the pVCA, a significant outcome predictor is already available in the hybrid laboratory. Subsequently the use of pVCA can facilitate deciding to Implant an additional MCD at an early stage.

2.7 Abkürzungsverzeichnis

pVCA	postinterventionelle Vena contracta area
MCD	Mitraclip Device
EVEREST	Endovascular Valve Edge-to-Edge Repair Study
NYHA	New York Heart Association
FMR	Functional Mitral Regurgitation
MI	Mitralinsuffizienz
TRAMI	Transcatheter mitral valve intervention registry
GRASP-IT	Getting Reduction of Mitral Insufficiency by Percutaneous clip implantation in Italy registry
3D-VCA	3 dimensional vena contracta area
EROA	Effective regurgitation orifice area

2.8 Literatur

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3. Erklärung des Eigenanteils an der Publikation

Eigenanteil

Thema, sämtliche Datenakquisition, Messungen der 3D-VCA prä und postinterventionell, Mitarbeit an der Verfassung des Manuskriptes

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5. Lebenslauf

Der Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt.

6. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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