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Defective recovery of QT dispersion following transcatheter aortic valve implantation: frequency, predictors and prognosis

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Abstract

Background Corrected QT dispersion (cQTD) has been correlated with non-uniform ventricular repolarisation and increased mortality. In patients with aortic stenosis, cQTD has been shown improved after surgical valve replacement, but the effects of transcatheter aortic valve implantation (TAVI) are unknown. Therefore, we sought to explore the frequency, predictors and prognostic effects of defective cQTD recovery at 6 months after TAVI. **Methods** A total of 222 patients underwent TAVI with the Medtronic-CoreValve System between November 2005 and January 2012. Patients who were on class Ⅰ or Ⅲ antiarrhythmics or on chronic haemodialysis or who developed atrial fibrillation, a new bundle branch block or became pacemaker dependent after TAVI were excluded. As a result, pre-, post- and follow-up ECG (median: 6 months) analysis was available in 45 eligible patients. Defective cQTD recovery was defined as any progression beyond the baseline cQTD at 6 months. **Results** In the 45 patients, the mean cQTD was 47 ± 23 ms at baseline, 45 ± 17 ms immediately after TAVI and 40 ± 16 ms at 6 months (15% reduction, $P = 0.049$). Compared to baseline, cQTD at 6 months was improved in 60% of the patients whereas defective cQTD recovery was present in 40%. cQTD increase immediately after TAVI was an independent predictor of defective cQTD recovery at 6 months (per 10 ms increase; OR: 1.89, 95% CI: 1.15–3.12). By univariable analysis, defective cQTD recovery was associated with late mortality (HR: 1.52, 95% CI: 1.05–2.17). **Conclusions** Despite a gradual reduction of cQTD after TAVI, 40% of the patients had defective recovery at 6 months which was associated with late mortality. More detailed ECG analysis after TAVI may help to avoid late death.

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Keywords: Aortic stenosis; Conduction abnormalities; Left bundle branch block; Predictors; QT dispersion; Transcatheter aortic valve implantation

1 Introduction

The natural course of aortic stenosis (AS) is characterised by among others cardiac arrhythmia and sudden death in up to 34% of the patients.[1–3] Surgical aortic valve replacement (AVR) has shown to reduce the risk of sudden death.[3] Whether this also holds for patients who undergo transcatheter aortic valve implantation (TAVI), which are characterised by more advanced age and co-morbid conditions than patients who undergo AVR, remains to be elucidated. Consistent with the findings of Thomas, *et al*.,[4] we recently found that sudden death accounts for approximately 10% of all-cause 1-year mortality after TAVI.[5]

Although not *per se* cardiac in origin, it is conceivable that late sudden death may be explained or caused by abnormalities in ventricular repolarisation. Corrected QT dispersion (cQTD) can be used to assess disturbances in the homogeneity of ventricular repolarisation and may, therefore, help to identify patients who are at increased risk of unexplained late death.[6] An increased cQTD reflects inhomogeneity of ventricular repolarisation and is associated with an increased risk of cardiac death in patients with a variety of heart diseases.[6–9]

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A reduction in cQTD has been reported early after AVR most likely due to a reduction in afterload, improved coronary flow and early left ventricular mass regression.[10–12] Similar effects may be expected after TAVI, yet, as mentioned these patients are older with more comorbidities and may also have been exposed to a longer period of increased left ventricular afterload. We, therefore, sought to explore the changes in cQTD and the frequency, predictors and prognostic effects of defective cQTD recovery at six months after TAVI.

2 Methods

2.1 Patients and procedure

Between November 2005 and January 2012, a total of 222 consecutive patients with AS underwent trans-arterial TAVI with the Medtronic CoreValve System (MCS). In all patients, a pre-, post- and follow-up 12-lead ECG was available. Patients with atrial fibrillation and those taking class I or III antiarrhytmics or on chronic haemodialysis were excluded.[13] For the purpose of an accurate assessment of cQTD changes over time, patients with a new conduction abnormality [left bundle branch block (LBBB), right bundle branch block (RBBB), or paced rhythm] immediately or six months after TAVI and those with a pre-existent conduction abnormality that progressed to a higher degree AV block were excluded as well. The final study population, therefore, consisted of 45 patients (Figure 1).

Details of the patient selection, prosthesis and subsequent phases of the transfemoral TAVI procedure have been previously published.[14–16] Briefly, all patients referred for TAVI were first seen on the out-patient clinic and then discussed in the heart team. Treatment decision was based upon consensus between an interventional cardiologist and a cardiac surgeon and since September 2010 by a team consisting of an interventional cardiologist, cardiac surgeon and a clinical cardiologist and/or an echocardiographist. Treatment decision was based upon a weighted assessment of risk and benefit of the various treatment modalities on the basis of all clinical and technical information of the patient. The procedure was performed with the patient under general anaesthesia with a temporary pacemaker wire positioned in the right ventricle and with default femoral arterial access through an 18F sheath. The aortic valve was first crossed under fluoroscopic control using a straight wire. This wire was exchanged for a stiff support wire followed by balloon valvuloplasty (22 or 23 mm × 4 cm) under rapid right ventricular pacing. The valve (available in 26, 29 and 31 mm) was then advanced over the aortic arch into the aortic annulus with a target deployment of 4–6 mm below the annulus.

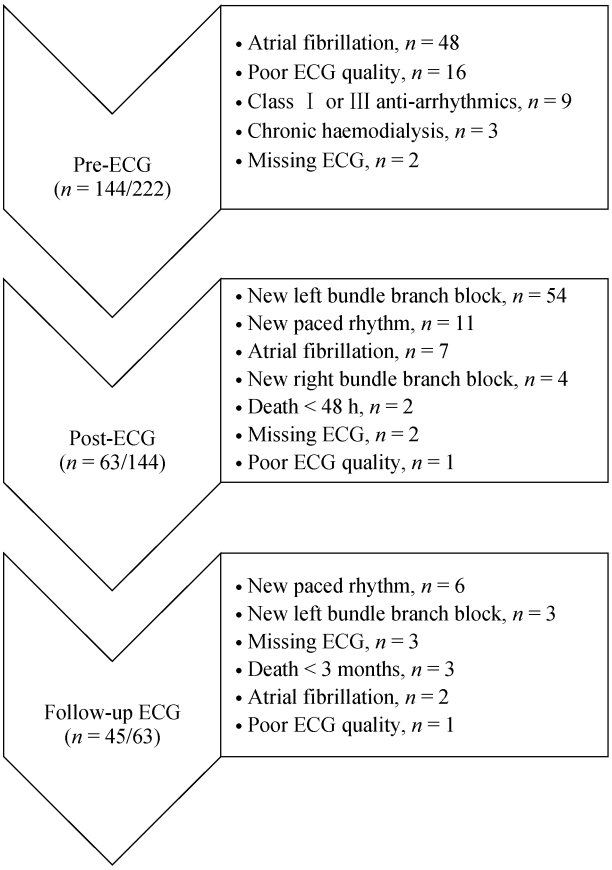

Figure 1. Flow diagram of ECGs available for serial analysis of pre-, post- and 6 month ECGs.

Patients were extubated before leaving the catheterization laboratory or within 2 h after arrival in the cardiac care unit.

2.2 Electrocardiographic recordings and measurements

All pre-, post- and follow-up [median: 181, interquartile range (IQR): 110-279 days] 12-lead ECGs were recorded at a paper speed of 25 mm/s and reprinted at a speed of 50 mm/s to improve sensitivity and accuracy of the manual measurements.[17,18] Inter-observer variability of cQTD measurements were evaluated by comparing the results of cQTD analysis between two observers who independently from one another analysed the ECGs. Inter-observer variability, expressed as the mean absolute difference between observers, was 8 ± 16 ms as determined in a consecutive series of 10 patients (30 ECGs). Intra-observer variability was 5 ± 8 ms.

The following time intervals were measured: PR, QRS, RR, QT and JT. The QT interval was considered to reflect the ventricular depolarization and repolarisation whereas the JT interval only reflects ventricular repolarisation because it does not encompass the depolarization phase.

The QT interval was calculated by measuring the beginning of the QRS complex until the visual return of the T

wave to the TP baseline. When a T wave was complicated by a U wave, the end of the T wave was defined as the nadir between the T and the U waves.[13] Intervals preceded by premature beats were not measured. For each lead, wherever possible, three consecutive cycles were measured and corrected for the heart rate using the Bazett's formula.[19,20] The average of the three consecutive cycles was used. The cJT interval for each interval was calculated by subtracting the QRS interval from the cQT interval.[21]

cQTD was calculated by measuring the cQT interval of all 12 ECG leads and defined by the substraction of the shortest from the longest interval (maximum minus minimum cQT interval).[6] In case of uncertainty of the definition of the end of a T wave, the lead disclosing this uncertainty was excluded from analysis. At least nine measurable leads were required for the purpose of this study. No attempt was made to correct for missing leads.[22] Defective cQTD recovery was defined as any progression beyond the baseline cQTD as assessed using follow-up ECGs. The cQTD variation (ΔcQTD) was calculated as the difference between cQTD before *vs*. after and before *vs*. 6 months after TAVI.[23]

Left and right bundle branch block was defined according to the Wold Health Organization and International Society and Federation for Cardiology Task Force.[24]

2.3 Follow-up

Follow-up information was collected during structured out-patient clinic visits after discharge. Survival and cause of death was obtained every 6 months by contacting the Dutch Civil Register and/or referring cardiologists and/or the general practitioners. Sudden and unexpected death was defined as a natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptoms in patients who were previously stable.[8]

2.4 Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared with the Chi square test or Fisher's exact test. The normality of distributions was assessed with the Shapiro-Wilk test. Normal and skewed continuous variables are presented as means ± SD and medians [interquartile range (IQR)], respectively. The Wilcoxon signed-rank test (for continuous variables) and the McNemar test conducted by exact methods (for categorical variables) were used to perform paired comparisons for pre-treatment *vs*. post-treatment and pre-treatment *vs*. follow-up ECG findings. Multivariable logistic regression including all variables with $P < 0.05$ in the univariable analysis was performed to determine the predictive factors of defective cQTD recovery. Given the small number of deaths during follow-up ($n = 7$), a univariable Cox regression analysis was performed to explore the potential association between defective cQTD recovery and late mortality. A two-sided $P < 0.05$ was considered to indicate significance and all statistical analyses were performed with SPSS software (version 17).

In accordance with the institutions policies, every patient gave written informed consent for TAVI and the use of anonymous clinical, procedural and follow-up data for research in accordance with Institutional Review Board approval. This study complies with the Declaration of Helsinki.

3 Results

The baseline characteristics and the serial ECG changes are summarized in Table 1 and 2, respectively. Overall, the

Table 1. Baseline characteristics of patients undergoing TAVI ($n = 45$).

Age, yr	78 ± 10
Men	26 (58)
Body mass index, kg/m^2	25.8 ± 3.8
New York Heart Association class ≥ III	37 (82)
Previous cerebrovascular event	12 (27)
Previous myocardial infarction	7 (16)
Previous coronary artery bypass graft surgery	13 (29)
Previous percutaneous coronary intervention	10 (22)
History of heart failure	18 (40)
Syncope	5 (11)
Diabetes mellitus	9 (20)
Hypertension	27 (60)
Peripheral vascular disease	5 (11)
Chronic obstructive pulmonary disease	16 (36)
Logistic EuroSCORE	12 (9–22)
Laboratory	
Serum sodium, mmol/L	141 ± 3
Serum potassium, mmol/L	4.4 ± 0.6
Serum creatinine, mmol/L	88 (77–112)
Medication	
Beta-blockers	22 (49)
Digoxin	1 (2)
Diuretics	23 (51)
Angiotensin converting enzyme inhibitors	13 (29)
Echocardiography	
Left ventricular ejection fraction, %	50 ± 13
Aortic valve area, cm^2	0.69 ± 0.2
Peak gradient, mmHg	75 27
Mitral regurgitation grade III or greater	3 (7)
Aortic regurgitation grade III or greater	7 (16)

Data are expressed as means ± SD, medians (IQR) or numbers (%). TAVI: transcatheter aortic valve implantation; IQR: interquartile range.

Table 2. Serial analyses of pre- post- and at follow-up ECGs after TAVI.

	Pre-treatment	Post-treatment	follow-up	*P*-value pre- *vs.* post	*P*-value pre *vs.* follow-up
Entire cohort, *n* = 45					
Heart rate, beats/min	70 ± 12	75 ± 13	72 ± 12	0.004	0.29
PR interval, ms	182 ± 28	188 ± 32	180 ± 23	0.33	0.74
QRS width, ms	124 ± 31	127 ± 31	124 ± 33	0.045	0.69
cJT interval, ms					
Minimum	285 ± 31	285 ± 24	287 ± 26	0.89	0.92
Maximum	332 ± 25	330 ± 25	327 ± 26	0.58	0.12
cQT interval, ms					
Minimum	417 ± 40	427 ± 36	422 ± 40	0.049	0.24
Maximum	464 ± 33	471 ± 35	462 ± 41	0.091	0.68
Dispersion	47 ± 23	45 ± 17	40 ± 16	0.82	0.049
Patients without conduction abnormalities, *n* = 27					
Heart rate beats/min	70 ± 14	74 ± 15	72 ± 13	0.051	0.48
PR interval, ms	183 ± 30	186 ± 34	177 ± 26	0.88	0.21
QRS width, ms	100 ± 8	105 ± 16	100 ± 10	0.045	0.92
cJT interval, ms					
Minimum	287 ± 33	287 ± 27	290 ± 27	0.64	0.86
Maximum	338 ± 23	334 ± 28	328 ± 25	0.27	0.052
cQT interval, ms					
Minimum	396 ± 30	405 ± 20	400 ± 27	0.22	0.47
Maximum	447 ± 24	452 ± 23	438 ± 26	0.21	0.16
Dispersion	50 ± 27	47 ± 16	38 ± 16	0.95	0.006

Data are expressed as means ± SD, medians (IQR) or *n* (%). TAVI: transcatheter aortic valve implantation; IQR: interquartile range.

average heart rate, QRS duration and minimum cQT interval increased immediately after TAVI, yet all changes returned to baseline values at 6 months. The cQTD decreased immediately after TAVI, with a further decline at 6 months (47 *vs*. 45 *vs*. 40 ms, $P = 0.049$). In a subgroup of 27 patients without conduction abnormality before, after and 6 months after TAVI, the cQTD decreased from 50 ms at baseline to 38 ms at 6 months (reduction of 24%, $P = 0.006$).

3.1 Frequency and predictors of defective cQTD recovery

In 27 out of the 45 patients (60%), a reduction in cQTD between baseline and follow-up was observed, whereas in 18 patients (40%) an increase was observed (defective cQTD recovery). The individual changes in cQTD are presented in Figure 2. Details of the baseline characteristics and perioperative results grouped according to the occurrence of defective cQTD recovery are shown in Table 3 and 4, respectively.

Patients with defective cQTD recovery had a worse ejection fraction (45% *vs*. 54%, $P = 0.026$), longer minimum cQT interval before TAVI (432 ms *vs*. 407 ms, $P = 0.001$) and an increase in cQTD immediately after TAVI (ΔcQTD: +13 ms *vs*. −13 ms, $P = 0.002$) in comparison to patients without defective cQTD recovery. The independent predictors of defective cQTD recovery are listed in Table 5.

3.2 Prognostic effects of defective cQTD recovery

The median follow-up was 14 months (IQR: 7–23); seven patients (16%) died at a median of 11 months (IQR: 6–15) after TAVI. Four deaths occurred in patients with defective cQTD recovery (cardiac death: 50%) and three deaths in patients without defective cQTD recovery (cardiac death: 0%). By univariable analysis, a higher baseline serum creatinine (per 10 mmol/L increase, HR: 1.09; 95% CI: 1.03–1.16) and defective cQTD recovery (ΔcQTD at 6 months, per 10 ms decrease, HR: 1.52; 95% CI: 1.05–2.17) were significantly associated with late mortality.

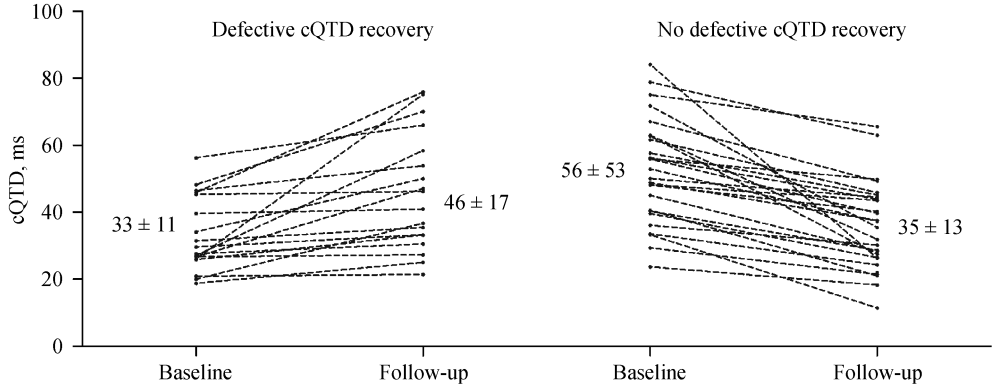

Figure 2. Individual changes in cQTD during follow-up according to the occurrence of defective cQTD recovery. cQTD: corrected QT dispersion.

Table 3. Baseline characteristics grouped according to the occurrence of defective cQTD recovery at 6 months after TAVI.

Variable	Defective cQTD recovery		
	No = 27	Yes = 18	*P*
Age, yrs	78 ± 10	79 ± 11	0.78
Men	13 (48)	13 (72)	0.11
Body mass index, kg/m^2	25.8 ± 3.7	25.8 ± 4.1	0.96
New York Heart Association class ≥ III	21 (78)	16 (89)	0.45
Previous cerebrovascular event	9 (33)	3 (17)	0.31
Previous myocardial infarction	2 (7)	5 (28)	0.098
Previous coronary artery bypass graft surgery	6 (22)	7 (39)	0.23
Previous percutaneous coronary intervention	7 (26)	3 (17)	0.72
History of heart failure	8 (30)	10 (56)	0.082
Syncope	4 (15)	1 (6)	0.63
Diabetes mellitus	4 (15)	5 (28)	0.45
Hypertension	15 (56)	12 (67)	0.46
Peripheral vascular disease	3 (11)	2 (11)	1.0
Chronic obstructive pulmonary disease	11 (41)	5 (28)	0.37
Logistic EuroSCORE	12 (8–21)	15 (10–25)	0.31
Laboratory			
Serum sodium, mmol/L	141 ± 4	141 ± 3	0.87
Serum potassium, mmol/L	4.5 ± 0.5	4.3 ± 0.6	0.33
Serum creatinine, mmol/L	82 (73–112)	91 (86–126)	0.084
Medication			
Beta-blockers	12 (44)	10 (56)	0.47
Digoxin	0	1 (6)	0.40
Diuretics	11 (41)	12 (67)	0.13
Angiotensin converting enzyme inhibitors	8 (30)	5 (28)	0.89
Echocardiography			
Left ventricular ejection fraction, %	54 ± 12	45 ± 13	0.026
Aortic valve area, cm^2	0.69 ± 0.2	0.68 ± 0.3	0.79
Peak gradient, mmHg	79 30	68 19	0.18
Mitral regurgitation grade III or greater	2 (8)	1 (6)	1.0
Aortic regurgitation grade III or greater	5 (19)	2 (11)	0.50

Data are expressed as means ± SD, medians (IQR) or *n* (%). cQTD: corrected QT dispersion; IQR: interquartile range; TAVI: transcatheter aortic valve implantation.

4 Discussion

In this study of 45 patients with aortic stenosis, we found that the average cQTD-time was significantly reduced at 6 months after TAVI. Yet, defective cQTD recovery was present in 40% of the patients. Worsening of cQTD immediately after TAVI was an independent predictor of defective cQTD recovery at 6 months, which in turn showed a directional signal of a higher risk of late mortality.

cQTD can be used to determine non-uniform ventricular repolarization and is increased in a variety of cardiac conditions such as long QT syndrome, chronic heart failure, hypertrophic cardiomyopathy, myocardial infarction and in patients with left ventricular hypertrophy associated with aortic stenosis.[6–9] In these patients, increased cQTD has been associated with susceptibility to ventricular arrhythmias, cardiac mortality and unexplained sudden death.[17] Yet, in patients with aortic stenosis, cQTD has been shown to reduce early after surgical aortic valve replacement, which is attributed to a reduced afterload, improved coronary flow and early left ventricular mass regression.[10–12]

Table 4. ECG and peri-operative results grouped according to the occurrence of defective cQTD recovery at 6 months after TAVI.

Variable	Defective cQTD recovery		
	No = 27	Yes = 18	*P*-value
Heart rate, beats/min			
Pre-treatment	70 ± 13	70 ± 10	0.90
Post-treatment	73 ± 14	77 ± 12	0.37
Follow-up	70 ± 11	74 ± 13	0.26
PR interval, ms			
Pre-treatment	183 ± 30	181 ± 25	0.85
Post-treatment	184 ± 33	193 ± 30	0.41
Follow-up	179 ± 21	181 ± 28	0.83
Minimum cJT interval, ms			
Pre-treatment	280 ± 34	292 ± 26	0.21
Post-treatment	290 ± 25	279 ± 22	0.12
Follow-up	292 ± 24	281 ± 28	0.17
Maximum cJT interval, ms			
Pre-treatment	336 ± 25	325 ± 25	0.17
Post-treatment	334 ± 28	324 ± 19	0.24
Follow-up	327 ± 23	327 ± 30	0.94
Minimum cQT interval, ms			
Pre-treatment	407 ± 39	432 ± 37	0.036
Post-treatment	427 ± 35	427 ± 38	0.99
Follow-up	420 ± 38	425 ± 44	0.69
Maximum cQT interval, ms			
Pre-treatment	463 ± 32	465 ± 36	0.81
Post-treatment	470 ± 36	473 ± 34	0.82
Follow-up	456 ± 35	471 ± 48	0.23
cQTD variation (pre *vs*. post-treatment), ms	−13 ± 31	+13 ± 31	0.002
cQTD variation (pre *vs*. follow-up), ms	−20 ± 24	+13 ± 13	< 0.001
Myocardial injury ≤ 48 h			
Maximum troponin T	0.22 ± 0.21	0.21 ± 0.20	0.93
Maximum CKMB	13 ± 16	8 ± 6	0.39
Echocardiography < 7 days			
Peak gradient	19 ± 9	18 ± 8	0.71
Mitral regurgitation grade III or greater	1 (4%)	2 (12%)	0.55
Aortic regurgitation grade III or greater	3 (12%)	1 (6%)	0.53

Data are expressed as means ± SD or *n* (%). CKMB: creatine kinase MB; cQTD: corrected QT dispersion; TAVI: transcatheter aortic valve implantation.

Table 5. Independent predictors of defective cQTD recovery after TAVI.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Left ventricular ejection fraction (per 10% decrease)	1.78 (1.04–3.03)	1.61 (0.84–3.09)	0.15
Pre-operative minimum cQT interval (per 10 ms increase)	1.20 (1.00–1.42)	1.12 (0.91–1.39)	0.28
cQTD variation (pre *vs*. post) (per 10 ms decrease)	1.98 (1.25–3.14)	1.89 (1.15–3.12)	0.012

cQTD: corrected QT dispersion; TAVI: transcatheter aortic valve implantation.

This has also been demonstrated in patients with severe congenital AS undergoing percutaneous balloon valvuloplasty.[25]

The findings of the present study indicate that cQTD recovery after TAVI does not occur immediately after the procedure but is a time related phenomenon that is not complete at 6 months (40% of the patients still had a defective cQTD recovery). This is in contrast with the findings of Sarubbi, *et al*.[25] who showed a 23% cQTD reduction immediately after balloon valvuloplasty and those of Tsai, *et al*.[11] who demonstrated a 48% reduction by 6 days after AVR.

The evident and immediate cQTD reduction following AVR contrasts with our findings of a delayed and incomplete cQTD reduction after TAVI. This can be explained by patient-related factors since TAVI patients are in general older than patients who undergo surgical valve replacement and, therefore, have more pronounced age-related degenerative changes of the myocardium. In addition, TAVI patients may suffer from longer periods of elevated afterload in comparison to surgical patients due to a longer time interval to clinical detection and treatment delay.[26,27] They may therefore, have more extensive cQTD and less response to early changes following afterload correction.

The observed increase in cQTD immediately after TAVI in patients with a defective cQTD recovery during follow-up could be due to an early impairment of the conductive system not appearing at the 12-lead ECG evaluation. In these particular patients, the reduction in afterload, improved coronary flow and left ventricular mass regression may not be sufficient to improve the cQTD at follow-up. This phenomenon could be particularly common after CoreValve implantation considering the frequent occurrence of new conduction defects associated with this device.[16] The latter may also explain why a significant number of patients had discordant cQTD changes (i.e., an initial decrease in cQTD from baseline to post-TAVI, followed by an increase at follow-up), which occurred in 46% of patients.

The prognostic value of cQTD is subject of debate.[17] Yet, some studies demonstrated that cQTD is strongly associated with malignant arrhythmias and cardiac mortality.[6,18] As mentioned, cQTD recovery was incomplete at six months in the present population. Although we lack the power to demonstrate an association with malignant arrhythmia and sudden cardiac death, it is conceivable that these patients are at increased risk of late sudden death. Of note, the causes of death in patients with defective cQTD recovery were sudden death (n = 1), myocardial infarction (n = 1) and terminal kidney failure (n = 2), whereas patients without defective cQTD recovery died because of a pneumonia (n = 1), sepsis (n = 1) and a perforated diverticulitis (n = 1). The clinical relevance of defective cQTD recovery was previously demonstrated by Chalil, *et al*.[28] who demonstrated that increased cQTD duration independently predicts sudden death/resuscitation in patients undergoing cardiac resynchronization therapy.

4.1 Limitations

cQTD is known to be an approximate of repolarisation abnormalities. Yet, given the absence of an underlying pathophysiologic explanation, the observation of (defective) cQTD recovery is of observational nature. We also acknowledge the fact that drugs other than class I or III antiarrhytmic drugs (i.e., antidepressants) may have affected the cQT recovery assessment and the fact that only quarter of the patients who underwent TAVI were eligible mainly because of the frequent occurrence of new conduction abnormalities associated with TAVI. Another limitation of the present study is that it cannot indicate which measures have to be taken in case of defective cQTD recovery. The question is whether one should first stop all drugs that may have such an effect or whether one even should consider the implantation of an automated implantable cardioverter-defibrillator. Data in larger series of patients stemming from multicenter observations are needed to confirm or to rule out the current observations, the precise timing and/or delay of recovery and to elucidate the role of potential measures to be taken. At last, the inter- and intra-observer variability of approximately 20% should be taken into account when interpreting the study results, and warrants future research to confirm our findings.

4.2 Conclusions

TAVI was associated with a gradual reduction of cQTD during the follow-up period. Defective cQTD recovery was seen in 40% of the patients. This was predominantly seen in patients with an increase in cQTD immediately after TAVI and was associated with a higher risk of late mortality. In addition to the regular follow-up examinations after TAVI, it is conceivable that more detailed analysis of the ECG may help to identify patients at risk of late unexpected death.

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