Heart Transplant Patients with Severe Cardiac Allograft Vasculopathy Have More Silent Ischemia and Non-Sustained Ventricular Tachycardia

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Abstract

Background: The incidence of sudden cardiac death (SCD) following heart transplantation (HTx) accounts for approximately 20% of post HTx deaths. Ischemia, brady- and tachy-arrhythmias caused by rejection and cardiac allograft vasculopathy (CAV) seem related to SCD. Hence, we aimed to investigate the relation between CAV, arrhythmias and silent ischemia in long-term HTx patients.

Methods: 49 HTx patients were included. Patients were CAV-classified in accordance with guidelines from International Society of Heart and Lung Transplantation. Patients were divided into predefined CAV groups (CAV 0, CAV 1, CAV 2 + 3). Incidences of arrhythmia and silent ischemia were detected by 48-hour electrocardiogram monitoring and analyzed blinded to CAV-status.

Results: Median time since transplantation was 9 years [4-14]. We observed a higher incidence of non-sustained ventricular tachycardia (NSVT) in CAV 2 + 3 patients than CAV 0 and 1 patients (p = 0.01). Likewise, isolated premature ventricular complexes (PVC) (p = 0.01) and PQ-interval prolongation (p = 0.01) were more frequent in CAV 2 + 3 patients than CAV 0 and 1 patients. Silent ischemia was only observed among CAV 3 patients (p = 0.04). We saw no significant difference in incidence of supraventricular tachycardia among CAV groups (p = 0.21). Likewise, no difference in right bundle branch block was observed (p = 0.68).

Conclusion: NSVT was associated with CAV-status in long-term HTx patients. Patients with moderate to severe CAV showed higher incidences of PVCs and PQ-interval prolongation than patients with mild or no CAV. Silent ischemia was only seen in patients with severe CAV. Nevertheless, implantation of cardioverter defibrillators (ICD) seems not warranted at this point.

Keywords

Heart transplantation, Cardiac allograft vasculopathy, Arrhythmia, Silent ischemia

Introduction

Heart transplantation (HTx) has revolutionized the treatment of end-stage heart failure, with median survival rates now exceeding 15 years [1]. Despite improvements in peri-operative care and long-term immunosuppression, HTx is still accompanied by unforeseeable hazards such as sudden cardiac death (SCD). While there has been a reduction in incidence of non-sudden deaths over the last decades, incidence of SCD has remained relatively constant and SCD accounts for approximately 20% of post HTx deaths [2].

CAV is an accelerated obliterative coronary artery disease characterized by a diffuse appearance and concentric thickening of the intimal vessel layer. CAV occurs frequently and affects approximately 50% of patients 10 years post HTx [3]. CAV is likely associated with SCD due to ischemia and arrhythmias caused by coronary spasms and progressive narrowing of the coronary vessels. In case reports, it has been observed that severe coronary spasms could present as global ischemia in the electrocardiogram (ECG) [4]. However, due to denervation, HTx patients seldom present with classic angina. It is of clinical relevance to uncover if a correlation between CAV and SCD is present, as pa-
tients with CAV may benefit from an implantable cardioverter defibrillator (ICD) to prevent SCD. However, so far guidelines do not recommend this treatment [5]. Hence, the present study is the first inventory of the incidence of silent ischemia and arrhythmias related to CAV in long-term HTx patients.

Methods

Study population

Consecutive patients > 18 years, transplanted at Aarhus University Hospital, Denmark before August 2017 were invited to participate, and enrolled after providing informed written consent in accordance with the principles of the Helsinki Declaration. Approval from The Danish Research Ethics Committee and The Danish Data Protection Agency was obtained (50589, 1-10-72-310-15).

Coronary angiography (CAG) was performed at the annual HTx follow-up visit. aECG monitoring was obtained in relation to CAG in most cases, but no more than 4 weeks after.

Exclusion criteria were cellular rejection (≥ 2R) or antibody mediated rejection < 3 months ago, severe renal failure (se creatinine > 250 µmol/l), severe anemia (se hemoglobin < 6 mmol/l), chronic obstructive pulmonary disease (forced expiratory volume in 1 sec < 50%), ventricular pace rhythm, persistent atrial flutter (AFL) or fibrillation (AF), left bundle branch block, acute myocardial infarction, percutaneous coronary intervention < 6 weeks ago, or ongoing digoxin treatment.

Fifty patients were enrolled. One patient was excluded due to loss of the ECG recorder. Hence, a total of 49 patients were included in the study.

Patient demographics were extracted from the Scandiatransplant database [6] and our local prospective database of HTx patients followed at the Department of Cardiology, Aarhus University Hospital, Denmark.

Ambulatory ECG monitoring

aECG monitoring was performed for 48 hours using a Holter recorder (Life Card CF digital Holter recorder Sentinel version 8.1, Spacelabs Healthcare, Washington, United States). Specially trained technicians, blinded to the result of the CAG, analyzed the ECGs using Pathfinder version P700. The primary investigators (KB, HE) examined and approved all ECG recordings. Medical treatment with β-adrenergic blocking agents, calcium antagonists, and nitrates were paused 1 week before and during recording.

ECG quality was evaluated by manual examination of the total recording. Mean heart rate (HR) was calculated from all RR intervals. Minimum and maximum HR was measured over 1 min.

QT-interval was estimated and corrected in relation to HR using the Bazett’s formula. Premature beats and tachyarrhythmia were diagnosed according to guidelines from European Society of Cardiology [5,7,8]. ST-segment deviation ≥ 100 µV lasting ≥ 1.0 min was considered diagnostic of silent ischemia [9]. Interpretation of silent ischemia with right bundle branch block (RBBB) was done in the lateral lead equivalent to V5 in the 12 lead ECG. PQ interval > 220 ms was defined as prolonged.

Coronary angiography

CAG was performed using a 6-french guiding catheter accessing the coronary arteries through the radial or femoral artery. Intracoronary nitroglycerin (250 µg) was administrated into the right and left main coronary arteries prior to imaging. At least two projections of each artery were acquired if possible.

Recordings were analyzed by a single investigator (KB) blinded to all other variables. From end-diastolic frames, all major branches with stenosis eyeballed > 30% were quantified using a 2-dimensional imaging program (2D-QCA; QAngioXA 7.3, Medis Medical Imaging, The Netherlands). Vessel contour was automated and manually corrected where needed. Maximal stenosis was calculated from vessel size proximal and distal to the lesion.

CAV status was defined by International Society of Heart and Lung Transplantation (ISHLT) standardized nomenclature [10]. Patients with percutaneous coronary intervention were classified as CAV 2 unless there was evidence of significant restrictive physiology, then they were classified as CAV 3.

Echocardiography

Echocardiography was performed according to guidelines from European Association of Cardiovascular Imaging [11]. A commercially available ultrasound system (Vivid E95,GE Healthcare Horten, Norway) with a 3.5 MHz phased array transducer (M5S) was used. Septal and posterior wall thickness, end-diastolic and end-systolic left ventricle (LV) diameter were measured in parasternal long axis view. Two-dimensional (2D) LV ejection fraction (EF) was based on the biplane method of discs [12]. LVGLS was obtained from frame-by-frame tracking of speckle patterns throughout the left myocardium. Segments with unacceptably low tracking quality were excluded. LVGLS was calculated semi automatically as the average longitudinal systolic strain of 17 myocardial segments [13]. Diastolic function was estimated using pulsed-wave Doppler for mitral inflow values; E and A velocity, deceleration time, isovolumetric relaxation time (IVRT) and tissue tracking for lateral e’ velocity. Diastolic dysfunction was defined in accordance with ISHLT guidelines [10]. Right ventricular function was estimated by use of tricuspid annular plane systol-
ic excursion.

Rejection

Biopsies were graded according to ISHLT guidelines [14].

For the statistical analysis, patients were divided into three rejection groups:

1. no rejection > 1R and < 50% of biopsies with 1R.
2. one ≥ 2R or > 50% of biopsies with 1R.
3. more than one ≥ 2R.

Statistics

Histograms and Q-Q plots were used to evaluate continuous data for normality. Non-parametric statistics and appropriate log-transformation was performed when necessary. Data is presented as median and interquartile range [IQR]. Categorical data are presented as absolute values or percentages. Between-group differences were assessed by ANOVA for normally distributed data and Kruskal-Wallis test for non-normally distributed data. A two-tailed p value of ≤ 0.05 was considered statistically significant.

Patients were divided into three predefined groups according to CAV severity: CAV 0, CAV 1 and CAV 2 + 3. Analyses were performed using STATA (StataCorp. 2017. Stata statistical software: Release 15. College Station, TX: StataCorp LLC).

Results

Patient demographics

A total of 49 HTx patients were enrolled from 1st May 2017 until 1st July 2018. Table 1 displays pa-

![Table 1: Demographics.](Image)

Data are presented median [IQR]. [p-value] = Combined estimate for all groups. HTx = Heart transplantation, ACE = Angiotensin converting enzyme, AT II = Angiotensin II receptor blocker, BNP = Brain Natriuretic Peptide, TNT = Troponin T, eGFR = Estimated glomerular filtration rate, HDL = High density lipoprotein, LDL = low density lipoprotein. [xx] presents combined p-value of all variables in the section.
Table 2: Left and right ventricular function by echocardiography.
Data are presented median [IQR]. LV = Left ventricle, LVEF = Left ventricle ejection fraction, EDV = End-diastolic volume, ESV = End-systolic volume, LA = Left atrium, IVRT = Isovolumetric relaxation time, GLS = Global longitudinal strain, TAPSE = Tricuspid annular plane systolic excursion, TR = Tricuspid regurgitation.

<table>
<thead>
<tr>
<th></th>
<th>CAV 0 (n = 26)</th>
<th>CAV 1 (n = 11)</th>
<th>CAV2+3 (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g/m²)</td>
<td>73.3 [56.6-90.1]</td>
<td>71.8 [60.8-98.9]</td>
<td>93.0 [69.5-133.8]</td>
<td>0.11</td>
</tr>
<tr>
<td>E/A, (ratio)</td>
<td>1.9 [1.5-2.2]</td>
<td>1.8 [1.4-2.1]</td>
<td>2.0 [1.7-2.3]</td>
<td>0.54</td>
</tr>
<tr>
<td>Deceleration time, (ms)</td>
<td>162 [143-187]</td>
<td>167 [146-185]</td>
<td>130 [114-141]</td>
<td>0.02</td>
</tr>
<tr>
<td>IVRT, (ms)</td>
<td>81 [74-87]</td>
<td>72 [66-93]</td>
<td>86.6 [68-94.5]</td>
<td>0.27</td>
</tr>
<tr>
<td>E/e´, (ratio)</td>
<td>10.5 [9.4-15.5]</td>
<td>10.1 [7.7-12.3]</td>
<td>14.9 [9.6-16.6]</td>
<td>0.17</td>
</tr>
<tr>
<td>LA volume, (ml)</td>
<td>38.5 [29.8-43.8]</td>
<td>34.0 [29.3-39.3]</td>
<td>43.9 [28.6-69.0]</td>
<td>0.32</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF Simpson biplane (%)</td>
<td>58 [57-61]</td>
<td>58 [56-63]</td>
<td>52 [43-58]</td>
<td>0.04</td>
</tr>
<tr>
<td>LV EDV (ml)</td>
<td>102 [88-132]</td>
<td>100 [94-112]</td>
<td>96 [90-156]</td>
<td>0.95</td>
</tr>
<tr>
<td>LV ESV (ml)</td>
<td>45 [39-54]</td>
<td>45 [39-51]</td>
<td>54 [38-79]</td>
<td>0.33</td>
</tr>
<tr>
<td>LV-GLS (%)</td>
<td>-18.0 [17.3-19.9]</td>
<td>-16.3 [15.8-19.8]</td>
<td>-14.0 [12.0-17.0]</td>
<td>0.003</td>
</tr>
<tr>
<td>Right heart function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>1.7 [1.4-2.0]</td>
<td>1.3 [1.1-1.9]</td>
<td>1.5 [1.0-1.7]</td>
<td>0.08</td>
</tr>
<tr>
<td>TR-gradient (mmHg)</td>
<td>19.3 [16.0-23.0]</td>
<td>21.0 [20.0-22.4]</td>
<td>23.1 [15.5-33.5]</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Table 3: 48-hour ambulatory ECG-monitoring.
Data are presented median [IQR]. ECG = Electrocardiogram, SDNN = Standard deviation of all normal RR intervals, sNN 6% = Number of successive RR interval differences > 6%, VT = Ventricular tachycardia, VT episodes and beats = Calculated if VT was present, PVC = Premature ventricular complexes, SVT = Supraventricular tachycardia, SVT episodes and beats = Calculated if SVT was present, PAC = Premature atrial complexes.

<table>
<thead>
<tr>
<th></th>
<th>CAV 0 (n = 26)</th>
<th>CAV 1 (n = 11)</th>
<th>CAV2+3 (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacemaker, n (%)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (bpm)</td>
<td>88 [82-93]</td>
<td>85 [80-92]</td>
<td>94 [84-97]</td>
<td>0.34</td>
</tr>
<tr>
<td>Minimum (bpm)</td>
<td>70 [62-79]</td>
<td>67 [61-72]</td>
<td>75 [68-83]</td>
<td>0.06</td>
</tr>
<tr>
<td>Maximum (bpm)</td>
<td>122 [115-128]</td>
<td>124 [114-135]</td>
<td>129 [112-139]</td>
<td>0.49</td>
</tr>
<tr>
<td>Prolonged PQ interval, n (%)</td>
<td>0 (0)</td>
<td>2 (18)</td>
<td>4 (33)</td>
<td>0.01</td>
</tr>
<tr>
<td>Prolonged QTc interval, n (%)</td>
<td>0 (0)</td>
<td>1 (9)</td>
<td>1 (8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Median QTc interval, ms</td>
<td>388 [369-418]</td>
<td>388 [367-447]</td>
<td>419 [374-427]</td>
<td>0.91</td>
</tr>
<tr>
<td>Right bundle branch block, n (%)</td>
<td>8 (31)</td>
<td>2 (18)</td>
<td>4 (33)</td>
<td>0.68</td>
</tr>
<tr>
<td>Silent ischemia, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (16.67)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurrence of VT, n (%)</td>
<td>1 (4)</td>
<td>2 (18)</td>
<td>5 (42)</td>
<td>0.01</td>
</tr>
<tr>
<td>Episodes if VT, n</td>
<td>1 [1-1]</td>
<td>2 [1-2]</td>
<td>1 [1-2]</td>
<td>0.72</td>
</tr>
<tr>
<td>Beats if VT, n</td>
<td>6 [6-6]</td>
<td>7 [4-9]</td>
<td>7 [6-8]</td>
<td>0.90</td>
</tr>
<tr>
<td>PVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beats, per 24 h</td>
<td>5 [2-28]</td>
<td>3 [1-8]</td>
<td>33 [11-55]</td>
<td>0.01</td>
</tr>
<tr>
<td>SVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occurrence of SVT, n (%)</td>
<td>10 (39)</td>
<td>3 (27)</td>
<td>8 (67)</td>
<td>0.13</td>
</tr>
<tr>
<td>Episodes if SVT</td>
<td>2 [1-3]</td>
<td>2 [2-177]</td>
<td>2 [1-4]</td>
<td>0.58</td>
</tr>
<tr>
<td>Beats if SVT</td>
<td>8 [4-11]</td>
<td>7 [4-32]</td>
<td>16 [12-811]</td>
<td>0.14</td>
</tr>
<tr>
<td>PAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beats per 24 h</td>
<td>9 [5-113]</td>
<td>4 [2-78]</td>
<td>7 [3-88]</td>
<td>0.67</td>
</tr>
</tbody>
</table>
tient demographics. The median age was 61 years [53-68] and the median time since HTx was 9 years [4-14]. Overall, 74% of the participants were males with an identical distribution of sex and age in the CAV groups. CAV 2 + 3 patients were transplanted significantly earlier that CAV 0 and 1 patients A (p = 0.01). No difference in New York Heart Association functional classification, body mass index, donor age, diabetes mellitus, hypertension or underlying condition for HTx was observed.

CAV 2 + 3 patients had higher values of N-terminal pro brain natriuretic peptide than CAV 0 and CAV 1 patients (p = 0.001). Furthermore, eGFR was significantly lower in the group with severe CAV (p = 0.03).

Overall, no difference in immunosuppressive treatment was observed. However, significantly more aspirin prescriptions were observed in CAV 2 + 3 patients compared with CAV 0 and CAV 1 (p = 0.002).

We observed no difference in previous rejection burden among the CAV groups (p = 0.7).

**Myocardial function by echocardiography**

Table 2 displays echocardiographic parameters. We observed no significant difference in LV diastolic function in terms of E/A, E/e’, IVRT, left atrial volume, and LV mass. However, deceleration time was significantly shorter in CAV 2 + 3 patients than CAV 0 and 1 patients (p = 0.02). LV systolic function was compromised in CAV 2 + 3 patients compared with CAV 0 and 1 patients. Thus, LVGLS was significantly lower in CAV 2 + 3 patients (p = 0.003). Also, LVEF was significantly reduced in patients with substantial CAV (CAV 0: 58% [51-61], CAV 1: 58% [56-63], CAV 2 + 3: 52% [43-58], p = 0.04).

We observed no significant difference in right ventricular function among CAV groups in terms of tricuspid annular plane systolic excursion (p = 0.08).

**Ambulatory 48-hour ECG recording**

Table 3 displays findings from the aECG recordings.

We observed no significant difference in quality of the recordings (p = 0.8). Likewise, no difference in pacemaker prevalence was observed (p = 0.1). Only dual chamber pacemakers had been implanted.

**Intracardial conduction and bradycardia**

Incidence of prolonged PQ interval seemed to depend on the degree of CAV (CAV 0: 0%, CAV1: 18%, CAV 2 + 3: 33%, p = 0.01). Prolongation of QTc interval was only observed in two patients and was not significantly different among the CAV groups (p = 0.30).

RBBB was observed in 29% of the participants with no difference among the CAV groups (p = 0.68), 21% had incomplete RBBB (0.10- 0.12s) and 79% had complete RBBB (≥ 0.12s).

No episodes of sinus bradycardia or sinus arrest were observed.

**Supraventricular arrhythmia**

No difference in occurrence of premature atrial complexes (PAC) was observed. An insignificant tendency for more SVT occurrence was observed in the CAV 2 + 3 group (CAV 0: 39% CAV 1: 27% CAV 2 + 3: 67%, p = 0.13).19% of SVT episodes were characterized as atrial fibrillation (AF), 10% as atrial flutter (AFL), the
remaining were characterized as atrioventricular reentry tachycardia, atrioventricular nodal reentry tachycardia or focal atrial tachycardia.

**Ventricular arrhythmia**

We detected significantly more premature ventricular complexes (PVC) in CAV 2 + 3 patients than CAV 0 and 1 patients (p = 0.01, Figure 1). Non-sustained ventricular tachycardia (NSVT) was observed more frequently in CAV 2 + 3 patients than CAV 0 patients (p = 0.01, Figure 2). If NSVT was present, the number of episodes and the number of beats per episode were not different among CAV groups (p = 0.72, p = 0.90).

No episodes of sustained VT were observed.

**Silent ischemia**

Two episodes of silent ischemia were recorded (aECG example; Figure 3). Both episodes occurred in CAV 3 patients (p = 0.04). Each patient had one episode of silent ischemia lasting 780 and 9 minutes, respectively. The ST-segment depression deviated 7 and 2 mm from the isoelectric line. Both patients had previously received percutaneous coronary intervention. They both died from cardiac arrest during the study period within 196 and 446 days from the aECG recording.

**Relation to rejection burden**

No difference in incidence of premature complexes or arrhythmia was found when comparing rejection groups (PAC: p = 1.0, PVC: p = 0.3, SVT: p = 0.4, VT: p = 0.1).

**Discussion**

This is to our knowledge the first study to investigate arrhythmias and silent ischemia systematically according to CAV status in long-term HTx patients. We found that CAV 2 + 3 patients had increased occurrence of NSVT compared with CAV 0 and CAV 1 patients. Furthermore, CAV 2 + 3 patients showed significantly more PVCs and silent ischemia.

No relation between rejection burden and rhythm disturbances was found.

No brady-arrhythmia or advanced atrioventricular block was detected.

**Non-sustained ventricular tachycardia and ventricular tachycardia**

In general, NSVT is common in HTx patients. In a cohort study of 25 patients assessed early after HTx, NSVT occurred in 60% and was associated with early rejection [15]. From our study in long-term HTx patients, 16% experienced NSVT but no clear relation to rejection burden was found. Chang, et al. retrospectively investigated arrhythmias in long-term HTx patients and observed NSVT in 8% of patients [16]. Hence, long-term HTx patients show substantially less NSVT than early HTx and chronic heart failure patients [17], but substantially more than healthy individuals as NSVT occurrence ranges from 0.5% to 1% in the healthy population [18].

It is likely that NSVT has a different clinical significance in HTx patients than healthy individuals or heart failure patients due to their cardiac denervation. Waxman, et al. found VT to be less inducible in sympathetic denervated rats [19]. On the other hand, cyclic vagus nerve stimulation was shown by Lee, et al. to have anti-arrhythmic effect on healthy rat hearts [20].

![Figure 2: Bar chart showing frequency of non-sustained ventricular tachycardia by CAV group.](image)
er, the relation between cardiac autonomic imbalance in HTx patients and NSVT is still left to elucidate.

**Arrhythmia and CAV**

Another mechanism predisposing to NSVT could be CAV. From our data, a significant correlation between CAV and NSVT was observed. Our findings are supported by a study that found CAV as the underlying mechanism in 33% of HTx patients with NSVT episodes [16].

Yamani, et al. showed that development of fibrosis after transplantation was associated with CAV [21]. Hence, the fibrous tissue seen with CAV could give rise to NSVT. In addition, the coronary disease per se involving both larger epicardial arteries and the microvasculature, may induce ischemia and thereby trigger NSVT.

Sustained VT was not observed in our study. This corresponds to earlier studies reporting sustained VT and ventricular fibrillation (VF) to occur in less than 2% of HTx patients [22]. Both NSVT and sustained VT are thought to have a strong impact on HTx prognosis [16].

Significantly more PVCs were observed in patients with CAV 2 + 3 than CAV 0 and 1. However, when comparing PVC burden in HTx patients to patients with heart failure, it was low [17]. Likewise, when comparing it to the PVC cutoff value for healthy individuals [23].

With the introduction of the bicaval transplantation method, SVT incidence has been significantly lowered when compared to the biatrial method [24]. SVT incidence seems highest early after transplantation where it is associated with acute rejection [25]. However, SVT was also the most common arrhythmia in our study population, occurring in 43% of the participants. Chang, et al. reported that 24% of long-term HTx patients had SVT with some degree of correlation to CAV [16]. These results correspond with our observations.

![Figure 3: aECG example showing beginning, max ST-segment depression, and ending of episode with silent ischemia.](image-url)
In several studies, the most common atrial arrhythmia was AF followed by AFL with respective incidences of 3% to 30% and 0.3% to 24% [26]. From our data, AF was seen in 19% and AFL in 10% of patients experiencing SVT.

**Silent ischemia and sudden cardiac death**

ST-segment depression was detected in two patients corresponding to 25% of CAV 3 patients.

ST-segment depression is strongly correlated to prognosis and mortality in patients with coronary artery disease (CAD) [27]. The same picture applied in our study with HTx patients; both patients with silent ischemia died within an average of 308 days from detection of ST-segment deviation. We did not have the chance to investigate the terminal rhythm in these patients. However, Vaseghi, et al. found that 61% of SCD in HTx patients were induced by ischemia, with asystole observed in 50%, pulse less electrical activity in 44%, and VF in 6% [28]. Based on the low incidence of VF combined with risk of infection and lead-related complications, Vaseghi, et al. concluded that ICD implantation was not warranted in SCD prevention in HTx patients. Only few reports exist about use and effectiveness of ICD-treatment after HTx. One study reported that 3.4% of patients received a post-transplant ICD for primary prophylaxis (severe CAV or sustained VT); 20% of these received appropriate device therapy [29]. A case series of two patients with severe CAV who were treated with ICDs and died from SCD, reported no ICD-shocks prior to death [30]. A clinical experience we have seen in our patients as well. Future studies on terminal rhythms associated with SCD and investigation of the therapeutic benefit of ICD-implantation and appropriate ICD-therapy is warranted.

It is known that coronary spasm can present as transient ischemia in both non-HTx and HTx patients [31]. Calcium-antagonists and nitrates present the mainstay of coronary spasm therapy. The medications reduce and prevent spasm attacks by inducing vasodilation. Furthermore, Diltiazem has been reported to reduce mortality after HTx [32]. Based on our observations, calcium-antagonists or nitrates could be suggested as a relevant treatment in CAV patients.

**Limitations**

This study is a single center study with a limited number of patients enrolled.

aECG monitoring was recorded for 48 hours. Longer intervals or more recordings would strengthen our results. However, ECG evaluation was conducted by personal blinded to CAV status.

A high proportion of patients presented with RBBB, potentially leading to underestimation of silent ischemia.

Five patients carried a pacemaker; none of the patients had constant ventricular pace rhythm.

CAG is an insensitive screening modality for CAV, as it is unable to visualize beyond the arterial lumen. Nevertheless, CAG in combination with echocardiography is the recommended screening-modality.

Prescribed nitrates, β- and calcium-antagonists were paused 1 week before and during ECG-recording. Discontinuation of β-antagonists could lead to rebound tachycardia. However, β-antagonist dose was low, limiting the risk of rebound tachycardia.

**Conclusion**

We observed a high incidence of NSVT with a significant overrepresentation in CAV 2 + 3 patients compared to CAV 0 and CAV 1 patients. Furthermore, patients with CAV 2 + 3 showed a higher incidence of PVCs compared with CAV 0 and 1 patients. Silent ischemia was only observed in patients with CAV 3. From our data, implantation of ICDs to prevent malignant arrhythmias causing SCD in CAV patients seems not warranted due to the short, self-limiting NSVT episodes and the low PVC burden.

No significant brady-arrhythmias were detected.

**Acknowledgements**

A special thanks to Karin Kirketerp, Annemette Wrang Christensen and the rest of the technical staff at Department of Cardiology who helped with and analyzed the 48-h aECG-monitorings. Thanks to Lene Konrad for helping with the echocardiographic recordings.

The study was generously supported by Aarhus University Research Fund. None of the authors have any conflicts of interest.

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