Assessment of Tp-Te Interval and Tp-Te/Qt Ratio in Patients with Aortic Aneurysm

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Abstract

BACKGROUND: Arrhythmic disorders in the aortic aneurysm (AA) have been rarely reported.

AIM: The study aimed to assess the repolarisation indices of ventricular arrhythmia (VA) (mainly Tp-Te interval and Tp-Te/QT ratio) in patients with AA.

METHODS: A group of 98 patients with AA and 75 patients as control were recruited. Many of indices of ventricular arrhythmia were assessed.

RESULTS: Many of indices like QT, QTc, QTpc, Tp-Te/QT, Tp-Te/QTc, Tp-Tec/QTc, S-Tp, S-Tpc, S-Te, S-Tec and fQRS were found to be significantly different in AA group (for all P < 0.05). However, QTp, mean Tp-Te and Tp-Tec were not found different (for all P < 0.05). Aortic diameter (Ao-D) was found to have a positive correlation with QTc, QTpc, S-Tp, S-Tpc, S-Te, S-Tec, fQRS (for all P < 0,05) and negative correlation with Tp-Te/QT (P = 0.047). The best cut-off level for prediction of Tp-Te ≥100 ms was found the Ao-D > 43.5 mm in ROC analysis (AUC: 0.69; P = 0.151) with sensitivity 60% and specificity 79.6%.

CONCLUSIONS: Although our study did not find any differences for mean Tp-Te interval between groups, many of other indexes of TDR were found to be significantly different. Ao-D was found to have significant correlations with many indices.

Introduction

Thoracic aortic diseases include degenerative, structural, acquired, genetic-based, and traumatic diseases of the aorta and aortic aneurysm (AA) is the main part of this conundrum whose diagnosis is made easily with transthoracic echocardiographic (TTE) study [1], [2]. AA had a complicated pathogenetic process with the degenerative formation and diminished significant aortic distensibility also with substantially increased of aortic wall stress and stiffness which has been demonstrated as a predictor risk factor of increased cardiovascular disease and arrhythmic events [3], [4], [5]. Although there are several case reports about

disorders of atrioventricular conductivity in AA with dissection complications, however there is not enough knowledge about arrhythmic disorders in patients with AA without rupture or dissection in the literature [6], [7]. On surface Electrocardiography (ECG) image T wave is inscribed by a sum of opposite voltage gradients in three different cell layers (Epicardial, M and endocardial cells) in the ventricular wall. Tpeak-Tend (Tp-Te) interval has been considering a measure of transmural dispersion of repolarization (TDR) and prolongation of Tp-Te (≥ 100 milliseconds [ms]) as well as QTc, QT and Tp-Te/QT ratio have been found of risk factors to develop cardiac arrhythmia especially ventricular arrhythmia (VA) and sudden cardiac death (SCD) in various cardiac disease also with normal healthy individuals [8], [9],

[10], [11], [12], [13], [14]. Fragmented QRS (fQRS) is another important novel ECG risk predictor for electro-mechanical dyssynchrony, VA, SCD and poor prognosis in patients with HF and hypertrophic cardiomyopathy [15], [16]. So this study aimed to determine if mainly Tp-Te interval and other indices of TDR like QT, QTp, Tp-Te/QT and fQRS are significantly different in patients with AA compared to the healthy control group.

The study was completed between March 2017 and January 2018 with totally 173 patients. Ninety-eight patients with AA and 75 normal healthy persons were included. Baseline characteristics and history of diseases including of diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD) and as well as being on any treatment or diet were assessed at baseline. AA was evaluated according to previous guidelines with the upper limit of normal ascending aorta diameter was accepted 39 millimetres (mm) [1], [2]. Patients with prior pacemaker implantation, cancer, other major illnesses, abnormal thyroid function test, abnormal electrolyte values and on antiarrhythmic drug treatment due to may affect ECG images so make changes on T wave measurements were excluded.

Approval of the Ethics Committee

The study protocol was approved by the Ethics committee at AfyonKocatepe University, and informed consent was obtained from each patient.

ECG

All ECGs were recorded using a General Electric MAC 5000 (GE Healthcare, Milwaukee, WI, USA). All 12-lead ECGs were recorded at 25 mm/s with standard lead positions. After magnification by 200%, all indices were measured. To eliminate both interobserver variability and bias, all measurements were measured by a single observer who was blinded to all clinical findings. QT intervals were taken to be from the onset of the QRS complex to the end of the T wave. The Tp-Te interval was defined as the interval from the peak of the T wave to the end of T wave [17]. Q-Tpeak (QTp) was measured from the onset of QRS to the peak of the T wave (Figure 1). The Tp-Te value reported was the average value of obtained in all precordial leads. The Tp-Te/QT ratio was calculated as the ratio of Tp-Te in that lead to the corresponding QT interval. Other novel indices were described as S-Tend (S-Te) interval and S-Tpeak interval (S-Tp). S-Te and S-Tp were measured from nadir of S wave to peak of T wave and end of T wave in precordial limbs. Bazett's formula (n/RR) was applied to all the indices to find heart rate corrected form (c: heart rate corrected) [18].
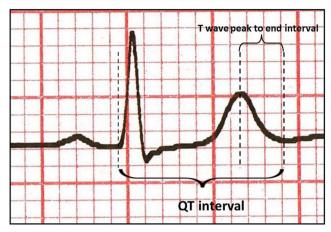

Figure 1: Demonstration of the T wave peak to end and QT intervals [17]

fQRS included various RSR patterns and was defined by the presence of an additional R wave (R prime), a notch in the nadir of the S wave, notch of the R wave, or the presence of more than one R prime (fragmentation) in two contiguous leads corresponding to a major myocardial segment [15].

Echocardiography

A Vivid 5 pro echocardiographic unit (GE, USA) with 3.5 MHz probe was used. The echocardiographic study was performed in standard position and standard measurements (M-mode, two-dimensional and Doppler echocardiography), were performed and/or reviewed by experienced staff cardiologists, compliant with the recommendation of the American Society of Echocardiography. Mitral inflow was determined by continuous and pulse wave Doppler echocardiography at the tips of the mitral leaflets. Early diastolic mitral peak flow velocity (E), late diastolic mitral peak flow velocity (A), E/A ratio were measured. Left ventricular diastolic dysfunction (LVD-Dys) was defined as a mitral continuous-wave (CW) Doppler E < A as stated in previous guidelines [19], [20].

Statistical analysis

Continuous variables were expressed as mean ± SD (Standard deviation), and categorical variables were presented as frequencies (%, per cent). Continuous and categorical measures were compared with *t*-tests or 2 statistics, as appropriated. For correlations, appropriate calculations were done. A *p* value < 0.05 was accepted as a statistically significant. All analyses were performed using SPSS Version 16.0 (SPSS Inc. Chicago, IL, USA).

Results

A group of 173 patients were included in our study (98 patients with AA and 75 patients in the control group). Some of the baseline features were displayed in Table 1 and 2.

Table 1: Baseline characteristic features and echocardiographic measures of groups

Baseline Features	Counts	Patients (n = 98. 100%)	Control (n = 75. 100%)	Total (n = 173. 100%)	p^*
Women	Count & percent in total	42 (24.2%)	24 (13.8%)		0.145 .
Male	Count & percent in total	56 (32.2%)	51 (29.4%)		
Age	Mean ± SD	70 ± 13.9 (min = 31. max = 96)	43 ± 10.5 (min= 28. max= 81)		< 0.0001 .
S- BP (mmHg)	Mean ± SD	138 ± 20.9	118 ± 10.7		< 0.0001 #
	Median (25%-75%)	140 (120-160)	120(110-130)		
D-BP (mmHg)	Mean ± SD	73 ± 10.7	68 ± 7.4		0.005 #
	Median (25%-75%)	80 (70-80)	70 (60-70)		
Pulse rate (per minute)	Mean ± SD	84 ± 25.2	79 ± 13.0		0.610 #
	Median (25%-75%)	80 (68-100)	78 (71-90)		
LDL-chol	Mean ± SD	129.2 ± 42.3	139.1 ± 41.3		0.178 #
	Median (25%-75%)	127 (98-158)	131.5 (110.5-171.2)		
Glucose	Mean ± SD	116.7 ± 32.4	97.5 ± 9.1		< 0.0001 #
	Median (25%-75%)	104.5 (95-124.5)	98 (91-104)		
BUN	Mean ± SD	27.2 ± 18.9	13.2 ± 3.1		< 0.0001 #
	Median (25%-75%)	21 (15-32.4)	13 (11-15)		
DM	Count and % within total population	28 (16.1%)	0 (0%)		< 0.0001 .
Hypertension	Count and % within total population	73 (42.1%)	0 (0%)		< 0.0001 .
CAD	Count and % within total population	33 (19.0%)	0(0%)		< 0.0001 .
LVEF %	Mean ± SD Min: 18 Max: 58	53 ± 9.3	60 ± 0		< 0.0001 #
	Median (25%-75%)	60 (47-60)	60 (60-60)		
LVDD (mm)	Mean ± SD	50 ± 7.3	46 ± 4.7		< 0.0001 #
	Median (25%-75%)	51 (46-54)	46 (44-50)		
LVSD (mm)	Mean ± SD	32 ± 8.1	28 ± 4.7		0.01 #
	Median (25%-75%)	32 (27-39)	28 (25-32)		
IVS (mm)	Mean ± SD	10 ± 1.8	9 ± 1.1		< 0.0001 #
	Median (25%-75%)	11 (9.5-12)	10 (9-10)		
Ao-D (mm)	Mean ± SD	41.8 ± 3.0 (min = 39. max = 54)	27.8 ± 3.2 (min = 20. max = 35)		< 0.0001 #
	Median (25%-75%)	41 (39-43)	27 (26-31)		

. : Chi-Square test. #: Independent samples non-parametric Mann-Whitney U test. *:P < 0.05 is accepted statistically significant. SD: Standard deviation, mm: millimeter, S-BP: Systolic blood pressure, D-BP: Diastolic Blood pressure, LDL-chol: LDL cholesterol, BUN: Blood Urea Nitrogen, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, LVEF: Left ventricular ejection fraction, LVDD: Left ventricular end-diastolic diameter, LVSD: Left ventricular end-systolic diameter, IVS: interventricular septum, Ao-D: Aortic diameter.

Many baseline parameters were found to be significantly different in AA group comparing to control group except LDL cholesterol (LDL-chol) and pulse rate (for LDL-chol $P = 0.178$; for pulse rate $P = 0.610$ and all others $P < 0.05$).

Table 2: Comparing to some of ECG features and mitral E/A ratio between groups

Features	Counts	Patients (n = 98)	Control (n = 75)	Total (n = 173)	p^*
PW (mm)	Mean ± SD	15.8 ± 5.4	9.2 ± 1.1		< 0.0001 #
	Median (25%-75%)	11 (9-12)	10 (8-10)		
LA (mm)	Mean ± SD	41.7 ± 7.2	34.3 ± 4.6		< 0.0001 #
	Median (25%-75%)	41 (36.2-46)	35 (32-37.7)		
RV (mm)	Mean ± SD	27.7 ± 5.6	28.4 ± 4.4		0.382 #
	Median (25%-75%)	27 (24-31)	28 (25-32)		
RA (mm)	Mean ± SD	30.3 ± 7.3	29.9 ± 4.8		0.792 #
	Median (25%-75%)	30 (23.2-35)	29 (27-33.2)		
P time (ms)	Mean ± SD	77.4 ± 42.1	86.8 ± 17.0		0.656 #
	Median (25%-75%)	80 (67.5-110.5)	80 (80-100)		
QRS time (ms)	Mean ± SD	88.0 ± 12.8	85.4 ± 10.7		0.111 #
	Median (25%-75%)	86 (80-100)	80 (80-94)		
T time (ms)	Mean ± SD	132.9 ± 28.1	140.6 ± 27.2		0.061 #
	Median (25%-75%)	120 (120-160)	140 (120-160)		
QT time (ms)	Mean ± SD	367.5 ± 49.3	354.5 ± 30.4		0.016 #
	Median (25%-75%)	363 (343-392.5)	360 (320-364)		
E/A (missing in patients N = 44, in control n = 31)	E < A count & per cent in total	41 (23.6%)	11 (6.3%)		< 0.0001 .
	E > A count & percent in total	13 (7.5%)	33 (19.0%)		

. : Chi-Square test. #: Independent samples non-parametric Mann-Whitney U test. *:P < 0.05 is accepted statistically significant. SD: Standard deviation, mm: millimeter, ms: millisecond, PW: Left ventricular posterior wall, LA: Left atrium four-chamber diameter, RV: Right ventricular four-chamber diameter, RA: Right atrium four-chamber diameter, E/A: Early diastolic mitral peak flow velocity (E), late diastolic mitral peak flow velocity (A).

Mean ascending Ao-D was found 41.8 ± 3.0 mm in the AA group and 27.8 ± 3.2 mm in the control group ($P < 0.0001$).

Table 3: Comparing of TDR between groups with independent samples non-parametric Mann-Whitney U test

Ecg Features	Counts	Patients (n = 98)	Control (n = 75)	Total (n = 173)	p^*
QTc (ms)	Mean ± SD	423.5 ± 55.8	403.8 ± 35.1		< 0.0001 #
	Median (25%-75%)	422 (401.7-446.2)	404 (381-424)		
QTp (ms)	Mean ± SD	294.5 ± 49.6	279.6 ± 28.1		0.08 #
	Median (25%-75%)	296 (268-320)	280 (262-300)		
Tp-Te (ms)	Mean ± SD	71.7 ± 15.1	74.8 ± 14.4		0.111 #
	Median (25%-75%)	80 (60-80)	80 (70-80)		
Tp-Te ≥ 100 ms					0.382 #
QTpc (ms)	Mean ± SD	342.7 ± 38.3	318.8 ± 35.7		< 0.0001 #
	Median (25%-75%)	339 (317-360)	318 (295-341)		
Tp-Tec (ms)	Mean ± SD	84.0 ± 20.7	84.8 ± 16.3		0.497 #
	Median (25%-75%)	83 (71.7-97)	87 (74-94)		
Tp-Te/QT	Mean ± SD	0.196 ± 0.04	0.211 ± 0.038		0.011 #
	Median (25%-75%)	0.200 (0.166-0.222)	0.222 (0.187-0.232)		
Tp-Te/QTc	Mean ± SD	0.186 ± 0.11	0.186 ± 0.037		0.003 #
	Median (25%-75%)	0.177 (0.142-0.196)	0.194 (0.155-0.210)		
Tp-Tec/QTc	Mean ± SD	0.196 ± 0.04	0.208 ± 0.04		0.035 #
	Median (25%-75%)	0.202 (0.165-0.222)	0.220 (0.187-0.232)		
PR (ms)	Mean ± SD	123.6 ± 66.6	142.5 ± 71.7		0.288 #
	Median (25%-75%)	144 (118-160)	120 (120-160)		
RR (ms)	Mean ± SD	758.7 ± 211.6	142.5 ± 71.7		0.308 #
	Median (25%-75%)	736 (599.7-876.2)	760 (666-840)		

#: Independent samples non-parametric Mann-Whitney U test. *:P < 0.05 is accepted statistically significant. SD: Standard deviation, ms: millisecond, RR: Measurement between two consequent R wave interval. PR: Measurement between the beginning of P wave to beginning to Q wave. c: Heart rate-corrected form with Bazett's formula (n/RR), min: minimum, max: maximum.

Significantly differences were found to be between groups for posterior wall (PW) and left atrium diameter (LA), QT time and mitral E < A or E > A (for all $P < 0.05$), but not for right atrium (RA), right ventricular (RV) dimensions, P- time, QRS- time and T time (all $P > 0.05$). For TDR, significant differences were found to be between groups for QTc, QTpc, Tp-Te/QT, Tp-Te/QTc, Tp-Tec/QTc (for all $P < 0.05$) except QTp, Tp-Tec and Tp-Te (for all $P > 0.05$ in Table 3).
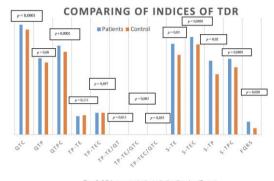
Table 4: Comparing of TDR between groups with independent samples non-parametric Mann-Whitney U and Pearson Chi-Square tests

Ecg Features	Counts	Patients (n = 98)	Control (n = 75)	Total (n = 173)	p^*
S-Tp (ms)	Mean ± SD	284.3 ± 34.1	231.6 ± 29.5		0.02 #
	Median (25%-75%)	254 (220-278.5)	234 (219-248)		
S-Tpc (ms)	Mean ± SD	291.2 ± 38.5	260.4 ± 30.6		< 0.0001 #
	Median (25%-75%)	281 (266.7-309)	265 (241-282)		
S-Te (ms)	Mean ± SD	348.6 ± 25.7	306.9 ± 30.6		0.03 #
	Median (25%-75%)	321 (294-350)	310 (280-320)		
S-Tec (ms)	Mean ± SD	375.1 ± 38.8	347.0 ± 34.1		< 0.0001 #
	Median (25%-75%)	370 (356.7-392)	346 (329-367)		
fQRS	Present count & percent in total	50 (28.9%)	25 (14.4%)		0.020 .
	None count & percent in total	48 (27.7%)	50 (28.9%)		

*: P < 0.05 is accepted as statistically significant. #: Independent samples non-parametric Mann-Whitney U test. .: Chi-Square test. S-Tp: Measurement from nadir S wave to T peak. S-Te: Measurement from nadir S wave to T end. fQRS: Fragmented QRS. SD: Standard deviation, ms: millisecond, c: Heart rate-corrected form with Bazett's formula (n/RR), min: minimum, max: maximum.

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When considering all patients with Tp-Te interval ≥ 100 ms, there wasn't any difference between groups (P = 0.382). Significant differences were also found to be between groups for S-Tp, S-Tpc, S-Teand S-Tec and fQRS (for all P < 0.05 in Table 4, and Figure 2).

In correlation analysis, Ao-D was found to have a positive correlation with QTc, QTpc, S-Tp, S-Tpc, S-Te, S-Tec and fQRS (for all P < 0.05 in Table 5). However negative correlation was found with Tp-Te/QT (r = - 0.158; P = 0.047).

Figure 2: Comparing of indices of TDR

To determine the best cut-off, point of Ao-D for prediction of Tp-Te ≥ 100 ms, analysis of ROC (Receiver Operating Characteristics) curves demonstrated cut-off level of Ao-Dwas to be determined > 43.5 mm with the area under the curve (AUC) was 0,69 (P = 0.151) and sensitivity 60%, specificity 79.6%.

Discussion

A histopathological feature of AA is based on degeneration of medial muscular (consisting of main proteins of collagen and elastin) layer of vessel wall [21]. Pathogenesis of AA includes aortic wall degeneration which has passive lumen dilation and active dynamic remodelling and stiffness of aorta also plays a major role as a contributor risk factor in this pathogenetic process as well as being a result of the progress of AA [22]. Aortic stiffness with other risk factors of AA has been accepted as a risk factor for increased major cardiovascular events and some arrhythmia [4], [5]. Some reports have been published about arrhythmic consequences of aortic disease especially acute aortic dissection [6], [7]. However, there is limited information about arrhythmic events and disorders in patients with AA without dissection. TDR within the ventricular myocardium has been suggested due to three electrophysiologically different cells, endocardial, epicardial and M cells [23]. The peak of the T-wave was shown to coincide with epicardial repolarisation and the end of the T-wave with repolarisation of the M cells so that Tp-e provides a measure of TDR [24]. Prolongation of indices of TDR like QTc, QTp, Tp-Te, Tp-Tec interval and Tp-Te/QT ratio has been suggested to provide of indexes of TDR and supposed to be risk factor of VA in various clinical scenarios like patients with Brugada syndrome (BS), hypertrophic cardiomyopathy, myocardial infarction with ST-Segment elevation and HF with low ejection fraction [12], [13], [14], [25], [26], [27], [28]. In these studies, various cut-off levels for Tp-Te values ≥ 100 ms have been proposed to predict the adverse outcome [27]. In our study mean ascending Ao-D was found higher in AA group (P < 0.0001). As the main part of our study, we found the significant differences between groups for indices of TDR like QTc, QTpc, Tp-Te/QT ratio, Tp-Te/QTc ratio and Tp-Tec/QTc ratio except for QTp, Tp-Tec. Interestingly, the mean Tp-Te interval was not found to be different between groups (P = 0.111). When considering to all patients with Tp-Te ≥ 100 ms, there wasn't any difference between groups (P > 0.05). Newer indices S-Tp, S-Tpc, S-Te, S-Tec and fQRS were found to be significantly different (for all P < 0.05).

Table 5: Correlation analysis of indices of TDR with Ao-D

		Age	LVEF	LVEDD	LVESD	Ao-D	BUN	Glucose	LDL-chol	DM	HT	CAD
QTc	r	0.291	-0.391	0.183	0.297	0.295	0.265	0.006	-0.146	0.169	0.220	0.186
	p	<0.0001	<0.0001	0.016	<0.0001	<0.0001	0.003	0.949	0.158	0.026	0.040	0.014
QTpc	r	0.298	-0.270	0.122	0.200	0.303	0.140	0.007	-0.180	0.100	0.223	0.166
	p	<0.0001	<0.0001	0.109	0.008	<0 .0001	0.116	0.937	0.081	0.189	0.003	0.029
Tp-Te/QT	r	-0.160	-0.050	0.055	0.056	-0.158	0.169	-0.043	-0.046	-0.029	0.159	-0.085
	p	0.036	0.515	0.474	0.464	0.047	0.057	0.646	0.661	0.705	0.037	0.267
Tp-Te/QTc	r	0.027	0.031	0.109	0.141	0.026	0.00	-0.128	0.011	-0.140	-0.137	-0.067
	p	0.722	0.688	0.152	0.064	0.741	0.999	0.164	0.918	0.065	0.072	0.380
Tp-Tec/QTc	r	-0.135	-0.062	0.072	0.071	-0.117	0.189	-0.024	-0.018	-0.009	-0.133	-0.078
	p	0.078	0.419	0.345	0.353	0.143	0.033	0.799	0.861	0.908	0.080	0.309
S-Tp	r	0.281	0.005	0.186	0.041	0.266	-0.118	-0.127	-0.050	-0.091	0.215	0.067
	p	<0.0001	0.946	0.014	0.597	0.001	0.186	0.168	0.630	0.234	0.005	0.382
S-Tpc	r	0.376	-0.231	0.134	0.198	0.370	0.115	0.008	-0.081	0.100	0.291	0.176
	p	<0.0001	0.002	0.079	0.009	<0.0001	0.199	0.934	0.437	0.191	<0.0001	0.020
S-Te	r	0.245	-0.009	0.253	0.062	0.228	-0.085	-0.187	-0.071	-0.109	0.199	0.079
	p	0.001	0.906	0.001	0.420	0.04	0.267	0.042	0.497	0.155	0.009	0.279
S-Tec	r	0.367	-0.324	-0.203	0.258	0.354	0.028	-0.005	-0.170	0.171	0.309	0.204
	p	<0.0001	<0.0001	0.070	0.001	<0.0001	0.716	0.956	0.100	0.024	<0.0001	0.007
fQRS	r	0.115	-0.284	0.034	0.149	0.203	0.076	0.132	-0.118	0.154	0.197	0.110
	p	0.132	<0.0001	0.635	0.051	0.010	0.393	0.153	0.256	0.043	0.009	0.151

LDL-chol: LDL cholesterol, BUN: Blood Urea Nitrogen, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, LVEF: Left ventricular ejection fraction, LVDD: Left ventricular end-diastolic diameter, LVSD: Left ventricular end-systolic diameter, Ao-D: Aortic diameter. HT: Hypertension.

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In correlation analysis, Ao-D was found to have a positive important correlation with QTc, QTpc, S-Tp, S-Tpc, S-Te, S-Tec and fQRS (all for $P < 0,05$) and negative correlation with Tp-Te/QT ratio ($P = 0.047$). To determine the best cut-off level of Ao-D for Tp-Te $\geq$ 100 ms interval, ROC (Receiver Operating Characteristics) curves demonstrated cut-off level > 43.5 mm with the area under the curve (AUC) was 0.69 ($P = 0.151$) and sensitivity 60%, specificity 79.6%.

Limitations: There are some important limitations to this study. This study was a cross-sectional study, and these findings need to further evaluate in a cohort study to find the importance of these indices for prediction of cardiovascular outcomes.

In conclusion, although our study did not find any differences for mean Tp-Te interval between groups many of other incidents of TDR were found to be significantly different. Ao-D was found to have significant correlations with many indices. Their clinical usages for prediction of adverse outcomes are needed to be assessed in the future.

Acknowledgements

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