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Original Article

Lipoprotein apheresis affects ventricular repolarization in patients with homozygous familial hypercholesterolemia

Lipoprotein aferezi homozigot ailevi hiperkolesterolemi hastalarında ventriküler repolarizasyonu etkiler

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Abstract

Aim: Patients with Homozygous Familial Hypercholesterolemia (HoFH) prone to experience premature cardiovascular disease and often die from sudden cardiac death (SCD) at a young age. Lipoprotein apheresis (LA) is the treatment of choice to prolong survival. Several mechanisms has been suggested to be responsible for the known short and long-term clinical benefits of this procedure. This study was conducted to assess the effect of single LA on ventricular repolarization parameters in patients with HoFH.

Material and Methods: Eleven patients (mean age 30.1 ± 5.5 years, male 63.6%) with HoFH on chronic LA treatment were enrolled in this preliminary study. Double filtration plasmapheresis (DFPP) was performed in all patients. To examine the effects of a single session of LA, on ventricular repolarization, the OT, QTc interval, the T peak-to-end (Tp-e) interval, Tp-e/QT and the Tp-e/QTc ratio were specifically calculated.

Results: The single session of LA reduced total LDL (from 10.04 ± 1.91 to 4.16 ± 1.21 mmol/L, P<001). The heart rate did not change significantly after LA session. Plasma levels of calcium and magnesium was significantly decreased after the procedure. The QTc decreased from 443.8 ± 23.3 ms to 412.3 ± 20.0 ms (P <0.001). The Tp-e interval and the Tp-e/QTc ratio decreased significantly [85 (70-89) ms vs. 63 (58-71)ms; P =0.003, and 0.19 (0.16-0.20) vs 0.15 (0.13-0.16); P =0.003, respectively].

Conclusion: Our data suggest that even a single session of LA improved electrocardiographic repolarization indexes.

Keywords: apheresis; arrhythmia; dispersion of repolarization; double filtration plasmapheresis; homozygous familial hypercholesterolemia

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Öz

Amaç: Homozigot ailevi hiperkolesterolemisi (HoAH) olan hastalar erken yaşlarda kardiyovasküler hastalığa yakalanma riski altındadırlar ve genellikle genç yaşta ani kardiyak ölüm (SCD) nedeniyle kaybedilirler. Bu hastalarda ömrü uzatmak amacı ile tercih edilen tedavi yöntemi lipoprotein aferezidir (LA). LA'nın kısa ve uzun dönem klinik faydalarından açıklamak için çeşitli mekanizmalar önerilmiştir. Bu çalışmada, HoAH'si olan hastalarda tek seans LA'nın, ventriküler repolarizasyon parametreleri üzerine olan etkisini araştırdık.

Gereç ve Yöntemler: LA uygulanan 11 HoAH hastası çalışmaya dahil edildi. Hastaların ortalama yaşı 30.1 ± 5,5 yıl ve hastaların %63,6'sı erkek idi. Tüm hastalara double filtrasyon plazmaferez uygulandı. İşlem öncesi ve sonrasında hastaların ventriküler repolarizasyon parametrelerinden OT, QTc aralığı, Tp-e aralığı, Tp-e / QT ve Tp-e / QTc oranı incelendi.

Bulgular: Tek seans lipoprotein aferezi LDL'yi anlamlı bir şekilde düşürdü (10.04 ± 1.91'den 4.16 ± 1.21 mmol / L, P <001). İşlem sonrası plazma kalsiyum ve magnezyum seviyeleri anlamlı derecede azaldı. QTc 443.8 ± 23.3 ms'den 412.3 ± 20.0 ms'ye (P <0.001) düştüğü saptandı. Tp-e aralığı ve Tp-e / QTc oranları önemli ölçüde azaldı [85 (70-89) ms ile 63 (58-71) ms; P = 0.003 ve 0.19 (0.16-0.20) - 0.15 (0.13-0.16); P = 0,003, sırasıyla].

Sonuç: Verilerimiz, tek bir lipoprotein aferez seansının bile elektrokardiyografik repolarizasyon indekslerini iyileştirdiğini göstermiştir.

Anahtar Kelimeler: Aferez, aritmi, çift filtrasyon plazmaferez, homozigot ailesel hiperlipidemi, repolarizasyon dispersiyonu

Introduction

Homozygous Familial Hypercholesterolemia (HoFH) is a rare inherited disease characterized by lethally high levels of low-density lipoprotein cholesterol (LDL-C) from birth [1] . Individuals with HoFH tend to experience accelerated atherosclerosis, premature development of cardiovascular disease (CVD) and often die from sudden cardiac death (SCD) at a young age [2].Lipoprotein apheresis (LA) is currently the gold- standard treatment to prevent fatal early CVD [3] in patients with HoFH. Although, a significant benefit on morbidity and mortality induced by LA has been proven, the underlying pathophysiological mechanisms of action are still unclear. In addition to the lipid-lowering effect, soluble peptides and proteins modulating thrombosis, inflammation and hemostasis are also removed to some degree by LA [4]. Evidence has been published showing that LA has specific pleiotropic effects on coagulation system, blood viscosity, inflammation, oxidative stress, endothelial function, coronary perfusion, vascular tone, thereby modulating the individual cardiovascular risk [5-7]

Besides conventional risk factors of SCD in the general population, HoFH patients have apparent underlying pathologies which may predispose them to untoward events and they are characterized by a pro-arrhythmic substrate because of the high prevalence of ischaemic heart disease, left ventricular hypertrophy, autonomic neuropathy, inflammation, myocardial systolic and diastolic dysfunction [2,8]. Recently, several noninvasive met[[hods have been employed to predict the occurrence of serious ventricular arrhythmias and establish patients at high risk for SCD, including QT interval, QT dispersion (QTd) and transmural dispersion of repolarization [9-10].

In the literature, studies conducted on patients with HoFH on chronic LA therapy mainly focused on different LA therapies, acute and chronic pleiotrophic effects, lipid and non-lipid effects of LA. Arrhytmic risk, the value of ECG parameters of ventricular repolarization and the effect of LA therapy on these parameters in HoFH patients were not evaluated. Thus, in the current investigation we sought to investigate for the first time the acute effect of LA on electrocardiographic indexes of repolarization, given that increased heterogenity of repolarization is related to ventricular arrhythmias.

Material and Methods

Study population

Eleven subjects (mean age 30.1 ± 5.5 years, Male 63.6%) with HoFH, attending a regular lipoprotein apheresis session, were recruited in this preliminary study. Familial hypercholesterolemia was diagnosed on the basis of family history, serum cholesterol level and thickness of the Achilles tendon in all patients. None of the patients had the exclusion criteria (previous pacemaker implantation, bundle branch block, persistent or permanent atrial fibrillation, unmeasurable T waves, using antiarrhythmic drugs that prolong the QT interval). All patients were in a stable clinical condition. All patients were non-smokers and have no diabetes. The data for each patients including the cumulative interval since the first LA treatment, the time interval between LA treatments,

the duration of the treatments, plasma volume that was filtered per treatment was collected. Informed constents were collected from all patients.

Before the apheresis session a standard 12-lead electrocardiogram (ECG) recorded. A second ECG was immediately recorded after LA treatment. Blood was taken before and after apheresis for measurement of plasma electrolytes, albümin, protein, hematocrit, C-reactive protein (CRP), fibrinogen and serum lipids to reveal LA- induced acute difference. Pretreatment LDL-C levels, defined as LDL-C level on maximal drug therapy before commencing LA, were obtained from medical records of patients. LDLmax was the pre-session LDL concentration before apheresis session, LDLmin was the post-session value. Time-averaged LDL-cholesterol levels were calculated with the following formula: LDLmin + 0.73 (LDLmax-LDLmin), described by Kroon et al. [11].

Lipoprotein apheresis

In all patients, LA was performed using double filtration plasmapheresis (DFPP) with the "Afer Smart", manufactured by MEDICA S.P.A., Medolla (Modena) Italia, a multifunctional device for therapeutic apheresis, which uses a hollow fiber plasma seperator "PlasmaCure "with an effective surface area 0.6 m2 and a priming volüme of 55 ml and a plasma component separator "SelectiCure "with a surface area of 1.9 m2, both manufactured by 3M Deutschland GmbH, neuss, Germany. In this procedure, plasma was separated from blood cells by first fiber filter and then perfused through the second filter which selectively retains useful plasma components but discards larger molecular weight components including LDL-C. Anticoagulation was achieved with heparin. During each procedure, the plasma volume of patient was calculated according to the body weight. Duration of each LA apheresis was between 60 and 150 minutes, depending on the plasma volume treated.

Laboratory parameters

Peripheral venous blood samples from each subject were obtained from the antecubital vein immediately before and immediately after apheresis session. Blood samples were taken into standardized tubes including dipotassium ethylenedinitrilotetraacetic acid for complete blood count (CBC). Coulter Counter LH Series (Beckman coulter Inc., Hialeah, Florida) was used for CBC. Plasma levels of LDL-C, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), CRP, protein and albumine were evaluated using an automated chemistry analyzer (Aeroset, Abbott, USA) with commercially available kits (Abbott, USA). The LDL-C concentration was calculated using the Friedewald equation [12]. Fibrinogen was measured with a nephelometer (Behring, Vienna, Austria)

Electrocardiographic analysis

The resting 12-lead surface ECG was recorded at a paper speed of 25 mm/s in the supine position in all study subjects. All ECGs were scanned and transferred to a personal computer and then magnified by 400% to avoid error in measurements. Two independent electrophysiologists blinded to clinical details measured the QT and Tp–e intervals. Three consecutive beats in selected leads were measured manually and a mean value of three readings was calculated. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave where the T-wave returns the isoelectric line when available. In unavailable cases, the end of the T-wave was determined as the intercept between the isoelectric line and the tangential line drawn through the maximum slope of the T-wave. QTc was calculated from the QT, which is corrected for heart rate using the Bazett's formula: $QTc = QT\sqrt{}$ (R–R interval). The Tp–e interval was defined as the interval from the peak of T-wave to the end of the T-wave where the T-wave returns the isoelectric line when available. In unavailable cases, previously described same method was used (Figure 1). The Tp–e/QTc ratio was calculated from these measurements. Inter-observer and intraobserver variability were found to be less than 5%. This study was approved by the local ethics committee.

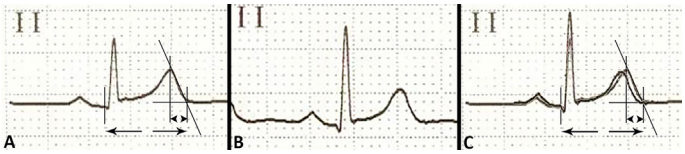

Figure 1. An ECG image shows measurement of repolarization parameters including QT (arrows) and Tp-e (arrow heads) intervals before LA (A). The second ECG image was obtained just after LA (B). In panel C, superimposed images from panel A and B are seen to demonstrate improved repolarization parameters related to LA.

Statistical analysis

Data were analyzed with the software SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were presented as mean ± SD and median with interquartile ranges as appropriate and categorical variables as frequency and percentage. To test the normality of distribution, Kolmogorov-Smirnov test was used. The Wilcoxon signed rank test was used for variables without normal distribution and the paired- T test for normally distributed variables. Spearman's correlation analysis was performed to examine potential associations between ECG indexes and various clinical and laboratory parameters. A two-tailed p-value of <0.05 was considered significant.

Results

The mean age of the patients in this study was 30.1 ± 5.5 years. Table 1 gives basal clinical characteristics and status of

major cardiovascular risk factors in the eleven HoFH patients involved in this study. Mean age at diagnosis was 10.1 ± 6.5 years. Cutaneous or tendinous lipid depositions were the first presenting symptom in seven patients and one patient was diagnosed during the screening for HoFH. All patients were on maximally-tolerated doses of statins (rosuvastatin: 40 mg/day, n :8) and ezetimibe (10 mg/day; n :8).

Table 1. BaselineCharacteristics of thestudysubjects

Characteristic	
Age, years± SD	30.1 ± 5.5
Male, n (%)	7 (63.6)
Hypertension, n (%)	1 (9.1)
Smoking, n (%)	0 (0)
Diabetes, n (%)	0 (0)
BMI (kg/m2) ± SD	25.3 ± 2.1
Consanguineousmarriage, n (%)	5 (45.5)
Age at diagnosis, years ± SD	10.1 ± 6.5
Age at firstcoronaryevent, years ± SD	21.5 ± 1.9
First symptom, n (%)	
Lipiddeposition	10 (90.9)
Screeningforfamilyhistory of FH	1 (9.1)
Coronaryarterydisease, n (%)	6 (54.5)
Aorticvalvestenosis, n (%)	
Mild	5 (45.5)
Moderate	3 (27.3)
Severe	1 (9.1)
Carotidarterydisease, n (%)	5 (45.5)
Stroke, n (%)	1 (9.1)
Periphericarterydisease, n (%)	6 (54.5)
Serum lipid profile, mmol/L ± SD Pretreatment on maximaldrugtherapy, beforestarting (LA)	
LDL-C	13.6 ± 2.6
Total cholesterol	15.9 ± 3.1
Trigliseride	3.5 ± 1.0
HDL-C	1.6 ± 0.6
Total Cholesterol/HDL-C	15.9 ± 3.1
Time-averaged LDL-c, mg/dl ± SD	8.4 ± 1.5
Age at first LA, years ± SD	25.4 ± 6.0
Frequency of apheresissessions, days± SD	19.0 ± 5.4
Cumulativeduration of apheresistreatment, months ± SD	52.6 ± 28.3
Proceduralduration, minutes± SD	123.6 ± 13.6
Plasmavolumepertreatment, mL± SD	2.781 ± 147

BMI=body massindex; FH= familialhypercholesterolemia; HDL-C=high- densitylipoproteincholesterol; LA=lipoproteinapheresis; LDL-C=low-densitylipoproteincholesterol; SD=standarddeviation

Note: Categorical data arepresented as absoluteandrelativefrequencies, whilecontinuousvariablesarepresented as means±standarddeviationsor as medianvalues (25th–75th percentile).

Early onset coronary artery disease (CAD) was present in 54.5% (six patients) of patients. The mean age at the time of the first coronary event was 21.5 ± 1.9 years None of them reported stroke or transient ischemic attacks. In all patients a noninvasive measurement of transvalvular aortic gradient was performed by a doppler method. In most of the cases (81.8%), the aortic valve was also affected; 9.1% had severe aortic stenosis (AS), 27.3% moderate and 45.5% mild AS. One patient had a history of aortic valve replacement. Dopler ultrasound of the carotid arteries revealed flow-reducing carotid stenoses in 5 patients. Lower extremity periferic artery disease was reported to be present in 6 (50%) patients. All of the patients had aortic atheroma plaques.

Information about therapeutic LA are listed in Table 1. All patients were on chronic LA treatment (mean 52.6 ± 28.3 months). Mean age at first LA was 25.4 ± 6.0 years. All of the patients were receiving LA treatment via vascular access (forearm arteriovenous fistulas in all). Mean frequency of apheresis sessions was every 19.0 ± 5.4 days. Mean LDL-cholesterol level was 13.6 ± 2.6 mmol/L on maximal drug therapy before starting LA.

Table 2 illustrates the changes that occurred in basic laboratory parameters after one LA procedure. A single LA therapy reduced circulating levels of total cholesterol, LDL-C, triglycerides, HDL-C by 59.1, 58.5, 48.7 and 42%, respectively ($P < 0.05$). There were significant decreases in fibrinogen, CRP, protein, albumin, ionized plasma calcium concentration and the level of plasma magnesium after LA ($P < 0.05$, for all). There was no significant difference between plasma hematocrit, potassium and WBC before and after LA ($p > 0.05$).

The results of the changes in measured ECG variables are shown on Table 2. During apheresis session the heart rate did not change significantly (pre LA; 79.4 vs post-LA; 75.5 bpm, $p > 0.05$). The QTc decreasesd from 443.8 ± 23.3 ms before LA to 412.3 ± 20.0 after LA ($P < 0.001$). The median value of Tp-e was 85 (70-89) ms before the beginning of LA, decreased to 63 (58-71) ms after LA treatment ($P = 0.003$). The Tp-e/QTc decreased from 0.19 (0.16-0.20) before LA to 0.15 (0.13-0.16) after LA ($P = 0.003$) (Figure 2). The correlation analysis failed to show any association between the baseline parameters and the baseline values of QTc, Tp-e and Tp-e/QTc or between the change of the laboratory parameters during LA and the corresponding change of the QTc, Tp-e and the Tp-e/QTc values.

Table2. Laboratorydataandrepolarizationparameters of thestudiedpopulation

Parameter	Beforesession	End of session	Pvalue
LDL-C, mmol/L	10.04 ± 1.91	4.16 ± 1.21	<0.001
HDL-C, mmol/L	0.7 (0.6-0.8)	0.4 (0.3-0.5)	0.001
Total cholesterol, mmol/L	11.5 ± 1.9	4.7 ± 0.9	<0.001
Triglyceride, mmol/L	3.9 ± 1.8	2.0 ± 0.8	0.008
Total choles-terol/HDL-C	15.5 ± 3.0	10.4 ± 1,9	0.001
Fibrinogen, mg/dl	2.4 ± 0.6	1.1 ± 0.4	<0.001
Hematocrit, %	44.1 ± 4.1	45.5 ± 4.7	0.073
CRP, mg/L	1.1 (0.4–1.4)	0.5 (0.2–0.7)	0.003
Protein, gr/dl	7.1 ± 0.3	5.3 ± 0.1	<0.001
Albumin, gr/dl	4.3 ± 0.1	3.6 ± 0.1	<0.001
Platelet, ×103	261.2 ± 81.2	232.2 ± 73.6	0.001
WBC, ×103	7.0 ± 1.5	7.7 ± 1.9	0.065
Creatinine, mg/dl	0.8 ± 0.1	0.7 ± 0.1	0.003
Potassium, mmol/L	4.0 ± 0.2	4.1 ± 0.1	0.647
Magnesium, mmol/L	0.8 ± 0.0	0.7 ± 0.0	0.006
Calcium, mmol/L	2.2 ± 0.1	1.9 ± 0.0	<0.001
İonizedCalcium, mmol/L	2.2 ± 0.0	2.0 ± 0.0	<0.001
Heart rate (bpm)	79.4 ± 11,8	75.5 ± 7,2	0.145
QT, ms	387 (378-400)	367 (362-373)	0.008
QTc, ms	443.8 ± 23.3	412.3 ± 20.0	<0.001
Tp-e,ms	85 (70-89)	63 (58-71)	0.003
Tp-e/QT	0.21 ± 0.0	0.17 ± 0.0	<0.001
Tp-e/QTc	0.19 (0.16-0.20)	0.15 (0.13-0.16)	0.003

CRP=c-reactive protein; HDL-C=high- densitylipoprotein-cholesterol; LDL-C=low-densitylipoproteincholesterol; SD=standarddeviation; WBC=whitebloodcell
Note: Significantchangesareshown in bold

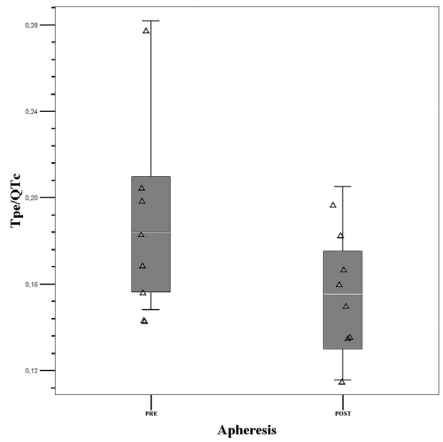

Figure 2. Box plotoverlaidwithdotplotshowingpatientlevel (smalltriangles) andmedian (whitelines) values of Tp-e/QTcbeforeandafterapheresis.

Discussion

In this study, we firstly demonstrated that a single session of LA significantly decreased ECG measures of ventricular repolarization including QT, QTc, Tp-e interval, Tp-e/QT and Tp-e/QTc ratio in HoFH patients.

Currently, there is a growing evidence to support the use of electrocardiographic repolarization markers to evaluate the risk of ventricular arrhythmias. The QT interval displays the sum of both ventricular depolarization (QRS) and repolarization (ST-T). The peak of the T wave (Tp) is thought to coincide with the end of repolarization of the ventricular subepicardium, while the end of the T wave (Te) is thought to correspond to the end of repolarization of the midmyocardium (M fibers). It is considered that the temporal difference between repolarization of mid-myocardium and sub-epicardium (Tp-e) represents, generally, heterogeneity of ventricular repolarization [9,10] . A prolonged QT interval has been shown to be closely associated with increased SCD risk in multiple medical conditions [13] . Recent studies indicated that the Tp-e interval, can be used as an index of the total (transmural, apico-basal, global) dispersion of repolarization. Also, increased Tp-e may be used as a predictor of ventricular tachyarrhythmias and cardiovascular mortality [14]. However, Tp-e/QT ratio appears to be a more sensitive arrhythmogenic index as it remains constant regardless of the dynamic variations in the heart rate and body weight. Taking into account the aforementioned considerations we aimed the measurement of the novel parameters QTc, Tp-e and Tp-e/QTc to evaluate the effects of LA on the dispersion of ventricular repolarization in patients with HoFH.

The mechanisms by which LA could exert beneficial effects on ventricular repolarization are not clear. Multiple benefits of LDL apheresis extend beyond the removal of LDL-C have been reported including improvements of blood viskosity, rheology, vascular tonus, endotel function as well as reduction of thrombosis ,oxidative stress and inflammation [15]. Several studies have demonstrated that simultaneous reduction of proinflammatory and prothrombotic factors together with atherogenic lipoproteins by long-term LA decreases lipid deposition on the arterial wall and stabilizes lipid- rich plaque [15,16]. Longitudinal trials demonstrated a significant reduction of cardiovascular risk and event rate and improvement of central, peripheral and cerebral perfusion under regular chronic lipoprotein apheresis treatment [16].

In contrast to such therapeutic benefits associated with long-term LA teraphy, Tamai et al. demonstrated that even a single session of LA apheresis in 7 patients improved endothelium-dependent vasodilatory response in forearm blood flow associated with increased production of nitric oxide (NO)

metabolites [17]. Similarly, Igarashi et al. demonstrated a significant immediate increase in acetylcholine-induced coronary endothelium-dependent vasodilation in both the epicardial artery and microcirculation after LA thetapy [18]. In adition, single LDL apheresis improved coronary microcirculation in patients with coronary artery disease and hypercholesteremia [19] .Furthermore, LA acutely decreases plasma viscosity and erythrocyte aggregation which contribute to decrease miyocardial infarction and sudden cardiac death [7]

It has been proposed that this potentially useful electrocardiographic acute alterations regarding ventricular repolarization is due to an acute improvement of the rheological properties and viskosity of blood, endotelial function, coronary perfusion and systolic function after the apheresis procedure. Alternative mechanisms involving inflammation and oxidative stress have also been suggested. Several studies have shown that electrocardiographic ventricular repolarization indexes are correlated with systemic inflammation [9]. On the other hand, LA therapy provides simultaneous reduction of proinflammatory and oxidative factors together with lipoproteins [5,7].

One of the possible mechanisms explaining the association between hypercholesterolemia and ventricular repolarization is "lipotoxic cardiomyopathy". In this theory, accumulated lipids in cardiomyocytes and lipid metabolites (eg ceramides, free fatty acids, lipid peroxides) lead to toxic effects via mitochondrial damage and sarcoplasmic reticulum stress [20-21] . Lin at al supported this hypothesis by showing that hypercholesterolemia reduces the level of connexin-43 protein, which is the major gap junction component; lowers myocardial conduction velocity thus impairs ventricular contractile function [22]. In patients with HoFH, this cardiac structural and functional changes can alter the repolarization and are at least partially an explanation for the improvement of repolarization parameters after LA therapy.

Our data also indicate that, although plasma levels of calcium and magnesium significantly decreased after LA therapy, ECG measures of ventricular repolarization including QTc shortened. The most commonly recognized effect of hypocalcemia on the ECG is prolongation of the QTc interval. Also, a decreased level of magnesium in plasma can also display itself as prolongation of the QTc interval on ECG [23]. This unexpected shortening in our study has mainly been attributed to changes in membrane fludity, due to high plasma cholesterol levels in HoFH patients. Hypercholesterolemia may influence the multiple plasma membrane functions which culminate in several pathophysiological patterns at cardiac and metabolic level [24]. Also, it has been shown to affect the structural and functional properties of myocardium. Particularly, it has been reported that differencess in membrane cholesterol content may change the activities of cardiac sarcolemmal enzymes (Na+/K+ ATPase and Ca2-stimulated ATPase and the Na+/Ca2+ Exchange) [25]. Such biophysical change can affect the permeability of different cations and to alter the enzyme activities of different membrane proteins [26].

An alternative explanation for the shortening of repolarization parameters is that apheresis removes the inhibition of endothelium-dependent relaxation caused by high LDL-C concentration in HoFH patients. Currently, there is a growing evidence to support that NO has a key role in mediating changes in QT interval and action potential duration (APD). In vitro [27] and in vivo [28] animal studies demonstrated that the rise in the NO activity is accompanied by the APD and QT interval shortening. The mechanisms responsible for the shortened APD were not clear. LA therapy cause to a significant reduction in oxidized LDL, which stimulate endothelial nitric oxide synthase activity, consequently rising production of NO. However, this interpretative theory remains to be assessed.

Though, increased ECG measures of repolarization are related to arrhythmic deaths, their prognostication in HoFH patients needs to be verified. We think that both metabolic and electrochemical alterations being frequently seen in HoFH patients influence action potentials causing repolarization anomalies represented by QT, Tp-e, and Tp-e/QT. Nevertheless, there are no prospective randomized studies examining the significance of these ECG parameters, and the true incidence of arrhythmic events is unclear.Further studies are needed to confirm whether these potentially beneficial effects, observed after single lipoprotein apheresis could also be achieved with currently available lipid-lowering treatments especially with pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in large amount of patients and for longer periods of time.

Limitations of the study

There are some potential limitations of this preliminary study. First, the study population was small in size due to the paucity of HoFH. The small sample size precluded us from making stratified analysis for gender and other subgroups. The effects of different treatment intervals, durations, the treated plasma volume and the different lipoprotein apheresis systems on ventricular repolarizasyon parameters were not addressed. It has been demonstated that LA modalities differ in their pleitrophic effects which may be relevant for outcome parameters not directly related to LDL removal. For ethical reasons, we could not justify performing LDL apheresis in healthy control subjects since there are substantial differences in a plenty of clinical and laboratory variables between healthy subjects and HoFH patients. Thus, we cannot say whether

LA also produces hemodynamic effects in the absence of hypercholesterolemia Hence, all our patients were receiving LDL apheresis for several years, our study may not represent the effects of early single apheresis sessions nor indicate longer term changes. Finally, we do not have long-term data with respect to clinical events and mortality to investigate the predictive value of the QTc, Tp-e interval and Tp-e/QTc ratio in patients with HoFH. Therefore, multicenter studies where greater numbers of patients on different apheresis modalities with long-term follow- up are needed to overcome all these limitations.

Conclusion

This study has been the first study searching the acute effects of LA procedure on electrocardiographic indexes which reflect heterogenity of ventricular repolarization and ventricular arrhytmias among patients with HoFH. Our findings revealed that even a single session of LA improved electrocardiographic repolarization indexes significantly. These results suggest that LA therapy may represent a protective effect on myocardium of these patient and it could therefore be speculated that the diminished heterogeneity of repolarization contributes to the lower incidence of malignant ventricular arrhythmias and SCD in HoFH patients on LA treatment

Declaration of conflict of interest

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