International Journal of Cardiology 168 (2013) 472–477

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications ☆

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ARTICLE INFO

Article history:
Received 2 May 2012
Received in revised form 10 September 2012
Accepted 22 September 2012
Available online 14 October 2012

Keywords:
Lamin A/C
Thromboembolic complications
Dilated cardiomyopathy
Platelets
Coagulation

ABSTRACT

Background: Lamin A/C (*LMNA*) mutation carriers suffer from a variety of clinical phenotypes, including dilated cardiomyopathy (DCM). Although it has been suggested that carriers are at risk for thromboembolic complications, it is unknown whether this risk is higher than can be expected from the underlying cardiac abnormalities. The purpose of this study was to determine whether a *LMNA* mutation is associated with an increased risk of thromboembolic complications.

Methods: We compared a cohort of 76 *LMNA* mutation carriers with a cohort of 224 idiopathic DCM patients without a *LMNA* mutation, with respect to the prevalence of arterial and venous thromboembolic complications. Furthermore, we carried out a case–control study to explore whether a prothrombotic phenotype was present in *LMNA* mutation carriers without DCM or atrial tachyarrhythmias ($n=14$) and compared this with mutation negative relatives ($n=13$).

Results: The prevalence of thromboembolic complications was higher in the cohort of *LMNA* mutation carriers than in DCM patients (22 vs 11%; $p<0.05$), after respectively mean follow-up of 42 ± 12 and 49 ± 12 years. After adjustment for possible confounders, including atrial tachyarrhythmias and left ventricular ejection fraction, *LMNA* mutation carriership was independently associated with an increased risk of thromboembolic complications (HR 4.8, 95% CI: 2.2–10.6). The results of the case–control study suggested a prothrombotic phenotype in *LMNA* mutation carriers, as reflected by an altered platelet function and increased thrombin generation.

Conclusions: LMNA mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. Laboratory research in *LMNA* mutation carriers without severe cardiac abnormalities suggests a prothrombotic phenotype.

1. Introduction

The *LMNA* gene encodes intermediate filament proteins lamin A and lamin C, which are components of the nuclear lamina [1]. Mutations in *LMNA* are related to more than a dozen different phenotypes, collectively described as laminopathies [2].

The majority of the pathogenic mutations in *LMNA* result in cardiac abnormalities, with or without muscular dystrophy [3,4]. The cardiac phenotype is characterized by conduction disorders, atrial and

Abbreviations: AA, arachidonic acid; AV-block, atrioventricular block; CI, confidence interval; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; HR, hazard ratio; *LMNA*, lamin A/C gene; LVEF, left ventricular ejection fraction; MPV, mean platelet volume; SD, standard deviation; TRAP, thrombin receptor activating peptide.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2012.09.118

ventricular arrhythmias, and dilated cardiomyopathy (DCM) [5]. The ventricular arrhythmias and DCM are often severe, and result in a poor prognosis of individuals carrying a *LMNA* mutation [6,7]. Apart from the cardiac morbidity an increased risk of thromboembolic complications has been suggested in anecdotal reports [8,9]. These reports, with a modest number of *LMNA* mutation carriers, are however inconclusive since it is unknown whether the observed events are higher than expected based on the cardiac abnormality (e.g. atrial fibrillation and/or DCM) per se [10–12].

Therefore, the aim of the present study was to determine whether a *LMNA* mutation is associated with an increased risk of thromboembolic complications, both arterial and venous. We carried out two different studies to investigate this. First, a cohort of *LMNA* mutation carriers was compared with a cohort of idiopathic DCM patients without a *LMNA* mutation, to verify whether a *LMNA* mutation is independently associated with an increased risk of thromboembolic complications. Secondly, we explored whether a prothrombotic phenotype was present in *LMNA* mutation carriers compared with mutation negative relatives.

2. Methods

2.1. Study designs

We carried out two different studies, i.e. a cohort and a case–control study.

2.2. Cohort study

The cohort study was a retrospective observational study, comparing a cohort of *LMNA* mutation carriers with a cohort of idiopathic DCM patients.

2.2.1. Cohort of LMNA mutation carriers

All consecutive individuals (probands and relatives) diagnosed with a pathogenic cardiac disease causing *LMNA* mutation, between January 2000 and December 2010, from two referral centers (the Academic Medical Center Amsterdam and the University Medical Center Groningen, The Netherlands), were eligible for the study. The definition of pathogenic *LMNA* mutation has been described previously [13].

2.2.2. Cohort of DCM patients

All consecutive individuals (probands), diagnosed with idiopathic DCM who were referred in the same period to the outpatient clinics of the clinical genetics departments of the same centers (and underwent *LMNA* screening), who did not carry a *LMNA* mutation were eligible for this cohort.

We only included individuals who were at least 16 years of age and who had been investigated by a cardiologist at least once. Clinical information about the cardiac and muscular phenotype and medical history were collected.

The principal outcome for the analysis was the composite end-point of either an arterial or venous thromboembolic complication.

Arterial thromboembolic complications were defined as ischemic stroke or transient ischemic attack diagnosed by a neurologist or acute peripheral arterial occlusion diagnosed by appropriate imaging.

Venous thromboembolic complications were defined as deep vein thrombosis or pulmonary embolism diagnosed by appropriate imaging.

2.3. Case–control study

All consecutive *LMNA* mutation carriers diagnosed with a pathogenic (cardiac disease causing) *LMNA* mutation and relatives who tested negative for the familial *LMNA* mutation between January 2000 and December 2010 in the Academic Medical Center, Amsterdam, The Netherlands, were eligible for this study. Individuals diagnosed with DCM with left ventricular ejection fraction (LVEF) ≤45% and atrial tachyarrhythmias or receiving vitamin K antagonists were excluded, to rule out their influence on the platelet and hemostatic characteristics. Complete medical history (including medication use), physical examination and blood analysis on platelet and hemostatic characteristics were carried out.

Several exploring platelet and hemostatic characteristics were assessed. Regarding the platelet characteristics, platelet number, mean platelet volume (MPV) and platelet function were measured. Flow cytometry (on a Calibur flow cytometer BD Biosciences) was performed to measure the basal and stimulated platelet activation (P-selectin) and monocyte–platelet complexes. Platelets were stimulated with arachidonic acid (AA, BIO/DATA Corporation, Horsham, PA) or thrombin receptor activating peptide (TRAP, Bachem AG, Bubendorf, Switzerland). Data were analyzed by CellQuest Pro (version 4.02; BD Biosciences).

The hemostatic characteristics were explored by measuring the end products of the coagulation cascade. We therefore, determined fragment 1+2 (marker for in vivo thrombin generation) and ex vivo thrombin generation, after stimulation with tissue factor (initiator of the coagulation cascade). Both the platelet and hemostatic measurements have been described previously [14,15].

The protocol was approved by the institutional review board of the Academic Medical Center, in Amsterdam, The Netherlands. All subjects provided written informed consent.

2.4. Risk factors for thromboembolic complications

2.4.1. Cardiac risk factors for thromboembolic complications

Atrial tachyarrhythmias were defined as paroxysmal (episode of atrial fibrillation for more than 30 s), persistent and permanent atrial fibrillation and atrial flutter. Atrioventricular (AV)-block was defined as a first (PR interval ≥0.20 s), second or third degree block. LVEF was determined by echocardiography, and defined as severely reduced (<35%), moderately reduced (35–55%), or normal (>55%). Cardiac device implantation was defined as both pacemaker and cardioverter defibrillator implantation.

2.4.2. Non-cardiac risk factors for thromboembolic complications

Hypertension was defined as a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg (or both) on at least two occasions or the use of antihypertensive medication. Diabetes mellitus was diagnosed based on the criteria of the American Diabetes Association or the use of antidiabetic drugs [16]. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Smoking was defined as current (case–control study) or current and former habitual (cohort study) daily use of 10 or more cigarettes. Oral contraceptive use was defined by current or former use of oral contraceptive for more than 1 year, during clinical follow-up by a cardiologist. Individuals were classified as having muscular dystrophy, when it was diagnosed by a neurologist.

2.5. Statistical analysis

The clinical characteristics in both studies were compared using the Student's *t*-test or Mann–Whitney *U* test for continuous variables (depending on whether the variable was supposed to be normally distributed) and the chi-square test in case of categorized variables expressed as proportions.

For the cohort study, we modeled time-to-event, from date of birth until an arterial or venous thromboembolic complication occurred (before the start of antiplatelet or anticoagulant therapy). Individuals were censored when antiplatelet or oral anticoagulant therapy was started (for any reason) or most recent evaluation in individuals without antiplatelet or oral anticoagulant therapy. Multivariate Cox regression analysis was used to assess the association between carrying a *LMNA* mutation and arterial and/or venous thromboembolic complications, independent of confounders for thromboembolic complications. Hazard ratios (HR) and 95% confidence interval (CI) were calculated; robust standard errors were calculated to account for family-clustering in the data [17,18]. Adjustments were made for known thromboembolic risk factors, including gender, cardiac device implantation, atrial tachyarrhythmias, oral contraceptive use, diabetes mellitus, smoking, hypertension, LVEF, AV-block and muscular dystrophy. Missing data were less than 10% per variable and imputed when necessary. Imputations were done randomly based on mean or median proportions of the complete group per variable.

For the case–control study, platelet and hemostatic characteristics were compared between *LMNA* mutation carriers and their mutation negative relatives, using mixed model analyses, with *LMNA* mutation carriers and their relatives as pairs.

The SPSS software version 17.0 (SPSS Inc., Chicago, Illinois) and the R statistical package (version 2.10.1) were used for analyses [19]. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Cohort study

3.1.1. Study population and characteristics

The cohort included 76 *LMNA* mutation carriers from 22 different families (range 1 to 24 individuals per family) and 224 DCM patients without a *LMNA* mutation (Table 1). *LMNA* mutation carriers were significantly younger than DCM patients (45 vs 51 years, $p<0.05$). Furthermore, *LMNA* mutation carriers had more often muscular dystrophy (33 vs 1%; $p<0.05$), atrial tachyarrhythmias (63 vs 21%; $p<0.05$), and conduction disorders (67 vs 14%; $p<0.05$) and a cardiac device was more often implanted (64 vs 51%; $p<0.05$) as compared with DCM patients. In contrast, the prevalence of a LVEF <35% (69 vs 17%; $p<0.05$) and prevalence of hypertension (19 vs 8%; $p<0.05$) were higher in DCM patients compared with *LMNA* mutation carriers. Other thromboembolic risk factors were similar between both groups.

Table 1
Cohort study: characteristics of *LMNA* mutation carriers compared with DCM patients.

	LMNA mutation carriers (n = 76)	DCM patients (n = 224)
Age—years	45 ± 13	51 ± 12*
Male	41 (54)	121 (54)
Thromboembolic complications	17 (22)	25 (11)*
Venous	6 (8)	9 (4)
Arterial	11 (14)	16 (7)
Dysrhythmias		
Atrial tachyarrhythmias	48 (63)	47 (21)*
AV-block	51 (67)	32 (14)*
LV function		
LVEF <35%	13 (17)	154 (69)*
LVEF 35–55%	22 (29)	70 (31)
LVEF >55%	41 (54)	0 (0)
Risk factors for thromboembolic complications		
Hypertension	6 (8)	43 (19)*
Diabetes mellitus	3 (4)	22 (10)
Smoking	27 (36)	74 (33)
Medication		
Oral anticoagulation and/or antiplatelet therapy	46 (61)	147 (66)
Oral contraceptive	3 (4)	1 (0)
Cardiac device	49 (64)	115 (51)*
Muscular dystrophy	25 (33)	2 (1)*
Pathogenic mutation		
LMNA	76 (100)	0 (0)
PLN	0 (0)	25 (11)[a]
MYH7	0 (0)	1 (0)
TPM1	0 (0)	1 (0)
TNNT1	0 (0)	1 (0)
SCN5A	0 (0)	1 (0)[a]

All variables are mentioned as number (%), except for age, which is mentioned as mean ± standard deviation (SD). AV-block = atrioventricular block, DCM = dilated cardiomyopathy, LV = left ventricular, LVEF = left ventricular ejection fraction, Smoking = former or current smoker.
* p-Value<0.05.
[a] One individual carried mutations in both genes.

3.1.2. Risk for thromboembolic complications

The prevalence of thromboembolic complications was significantly higher among *LMNA* mutation carriers compared with DCM patients (22 vs 11% respectively; p<0.05), after a respectively total follow-up of 3173 (mean follow-up of 42 ± 12 years) and 10,893 (mean follow-up of 49 ± 12 years) patient-years. In the largest family consisting of 24 *LMNA* mutation carriers 5 (21%) thromboembolic complications occurred, and in the remaining 52 *LMNA* mutation carriers from the other families 12 (23%) thromboembolic complications occurred. The prevalence of arterial thromboembolic complications was respectively 14 vs 7% and the prevalence of venous thromboembolic complications was respectively 8 vs 4%. The mean age of onset of thromboembolic complications was comparable between both groups, with a mean age of 45 ± 10 years for *LMNA* mutation carriers and 47 ± 12 years for DCM patients.

Carrying a *LMNA* mutation was associated with an increased risk of thromboembolic complications (HR 3.5, 95% CI: 1.9–6.7) (Table 2). This association remained present after adjustment for possible confounders (HR 4.8, 95% CI: 2.2–10.6) (Fig. 1). For the separate components of thromboembolic events, i.e. arterial and venous, the hazard ratios were also significant, respectively 5.6 (95% CI: 2.3–14.0) and 6.5 (95% CI: 1.7–25.8).

Since *LMNA* mutation carriers had a higher prevalence of atrial tachyarrhythmias, we also analyzed the data stratified for atrial tachyarrhythmias. In both strata, with and without atrial tachyarrhythmias, the *LMNA* mutation carriers had an increased risk of thromboembolic complications, with hazard ratios of respectively 6.0 (95% CI: 2.0–18.1) and 5.3 (95% CI: 1.9–14.8) (Fig. 2).

Table 2
Cox regression analysis of the cohort study: risk of thromboembolic complications in *LMNA* mutation carriers compared with DCM patients.

	Hazard ratio (95% CI)
Model 1	3.5 (1.9–6.7)*
Model 2	3.6 (1.9–6.9)*
Model 3	4.8 (2.2–10.6)*

Model 1: crude, Model 2: sex adjusted, Model 3: additionally adjusted for family-clustering, cardiac device implantation, atrial tachyarrhythmias, oral contraceptive use, diabetes mellitus, smoking, hypertension, LVEF, muscular dystrophy and AV-block. CI = confidence interval.
* p-Value<0.05.

3.2. Case–control study

3.2.1. Study population and characteristics

We included in total 27 individuals from 8 different families. This rendered us 14 individuals with a *LMNA* mutation and 13 mutation negative relatives. Table 3 displays the main characteristics of the case–control study population as well as the prevalence of risk factors for thromboembolic complications. In the 14 *LMNA* mutation carriers and 13 mutation negative relatives, baseline characteristics and risk factors for thromboembolic complications were comparable.

3.2.2. Platelet and hemostatic characteristics

Concerning the platelet characteristics (Table 4): *LMNA* mutation carriers had a decreased platelet count compared with relatives (205 vs 248×10^9/L, respectively; p<0.05). Furthermore, the MPV tended to be higher in *LMNA* mutation (11.2 vs 10.4 fL, respectively; p = 0.08). There was no difference with regard to the basal level of platelet activation, i.e. the platelet activation status in blood without an inducer. Upon stimulation with TRAP, however, the response of

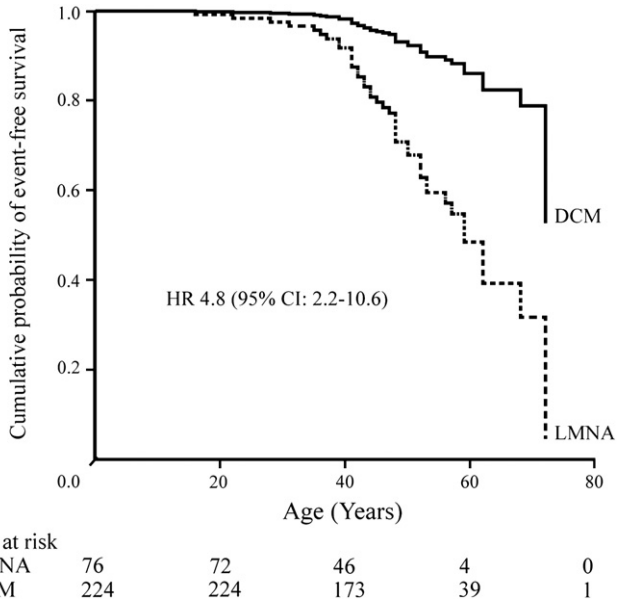

Fig. 1. Cohort study: event-free survival of *LMNA* mutation carriers compared with DCM patients. Survival curve of *LMNA* mutation carriers compared with idiopathic DCM patients corrected for confounders: family-clustering, cardiac device implantation, gender, atrial tachyarrhythmias, oral contraceptive use, diabetes mellitus, smoking, hypertension, LVEF, muscular dystrophy and AV-block. Follow-up in years of age, from date of birth until thromboembolic complication. In individuals without a thromboembolic complication the follow-up period was censored at the start of oral anticoagulant/antiplatelet therapy or most recent evaluation. CI = confidence interval, DCM = dilated cardiomyopathy, Event = occurrence of thromboembolic complications, HR = hazard ratio.

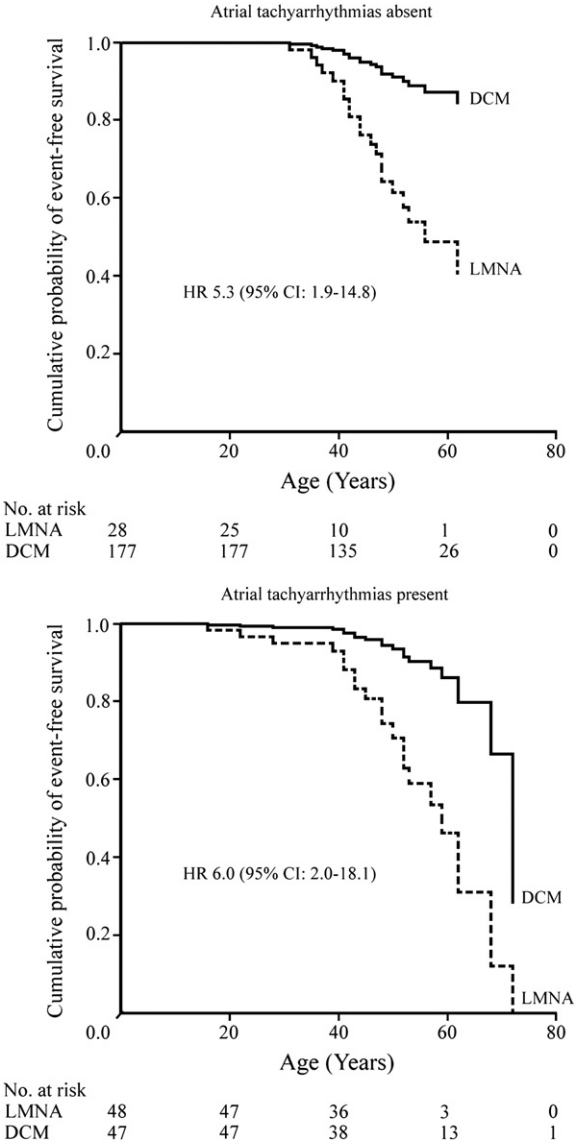

Fig. 2. Cohort study: event-free survival of *LMNA* mutation carriers compared with DCM patients stratified according to atrial tachyarrhythmias. Survival curve of *LMNA* mutation carriers compared with idiopathic DCM patients stratified according to atrial tachyarrhythmias and corrected for confounders: family-clustering, cardiac device implantation, gender, oral contraceptive use, diabetes mellitus, smoking, hypertension, LVEF, muscular dystrophy and AV-block. Follow-up in years of age, from date of birth until thromboembolic complication. In individuals without a thromboembolic complication the follow-up period was censored at the start of oral anticoagulant/antiplatelet therapy or most recent evaluation. CI = confidence interval, DCM = dilated cardiomyopathy, Event = occurrence of thromboembolic complications, HR = hazard ratio.

the platelets from *LMNA* mutation carriers was significantly lower (83 vs 94% P-selectin; $p<0.05$). Furthermore, the baseline number of monocyte–platelet complexes was not statistically different between *LMNA* mutation carriers and the relatives (12 vs 9 events; $p=0.41$). However, after stimulation the number of platelet–monocyte complexes in *LMNA* mutation carriers was significantly lower. The number of monocyte–platelet complexes after stimulation with AA was significantly lower in *LMNA* mutation carriers (60 vs 98 events, $p<0.05$).

Concerning the coagulation measurements (Table 4): The thrombin generation was significantly higher in *LMNA* mutation carriers, with a higher peak level (312 vs 273 nM, $p<0.05$) and higher velocity index (118 vs 91 nM/min, $p<0.05$). On the other hand, the prothrombin fragment 1 + 2 concentration, was comparable in both groups.

Table 3
Case–control study: characteristics of *LMNA* mutation carriers compared with mutation negative relatives.

	LMNA mutation carriers (n = 14)	Relatives (n = 13)
Age—years	41 (32–56)	39 (24–53)
Male	7 (50)	9 (69)
Thromboembolic complication	2 (14)	1 (8)
Arterial	1 (7)	1 (8)
Venous	1 (7)	0 (0)
LVEF		
45–55%	4 (29)	–
>55%	10 (71)	–
Risk factors for thromboembolic complications		
Hypertension	2 (14)	1 (8)
Diabetes mellitus	1 (7)	0 (0)
Current smoker	4 (29)	3 (23)
Body mass index—kg/m^2	26 (21–28)	25 (24–27)
Medication		
Antiplatelet therapy	1 (7)	1 (8)
Oral contraceptive	2 (14)	1 (8)

All variables are mentioned as number (%), except for age and BMI, which is mentioned as median (IQR). BMI = body mass index, IQR = interquartile range, LVEF = left ventricular ejection fraction. – Data not available. all p-values are > 0.05.

4. Discussion

The present study demonstrates that a *LMNA* mutation is associated with an increased risk of thromboembolic complications both arterial and venous. After adjustment for potential confounders including atrial tachyarrhythmias, the hazard ratio was approximately 5, with comparable ratios for the components of the thrombotic outcome separately.

4.1. Independent association between LMNA mutation and thromboembolic complications

DCM per se is associated with a high risk for thromboembolic complications due to left ventricular dilatation, decreased LVEF and atrial tachyarrhythmias [10,11,20]. However, the results from our study showed that the prevalence of both arterial and venous thromboembolic complications in *LMNA* mutation carriers was even higher than in idiopathic DCM patients. Noteworthy, the cohort of *LMNA*

Table 4
Case–control study: platelet and hemostatic characteristics of *LMNA* mutation carriers compared with mutation negative relatives.

	LMNA mutation carriers (n = 14)	Relatives (n = 13)
Platelets		
Platelets—10^9/L	205 ± 35	248 ± 54*
MPV—fL	11.2 ± 1.0	10.4 ± 1.0
Platelets activation—% P-selectin		
No inducer	4.7 ± 2.3	5.0 ± 3.0
AA 0.5 mM	59 ± 19	69 ± 13
TRAP 15 μM	83 ± 24	94 ± 4*
Monocyte–platelet complexes—no. of events		
No inducer	12 ± 11	9 ± 7
AA 0.5 mM	60 ± 33	98 ± 57*
TRAP 15 μM	155 ± 73	176 ± 55
Thrombin generation test		
Prothrombin fragment 1 + 2—pM	166 ± 79	156 ± 69
Peak—nM	312 ± 35	273 ± 58*
Time to peak—min	6.0 ± 0.8	6.5 ± 1.2
Velocity index—nM/min	118 ± 28	91 ± 40*

All variables are mentioned as mean ± standard deviation (SD).
AA = arachidonic acid, MPV = mean platelet volume, TRAP = thrombin receptor activating peptide.
* p-Value < 0.05.

mutation carriers included both probands and relatives, also including presymptomatic mutation carriers. We thus confirmed the earlier anecdotic reports by van Tintelen et al. and Boriani et al., both reporting a high prevalence of thromboembolic complications in *LMNA* mutation carriers [8,9]. Interestingly, carrying a *LMNA* mutation was associated with an increased risk for thromboembolic complications, independent of thromboembolic risk factors such as atrial tachyarrhythmias, LVEF and cardiac device implantation.

One might argue, whether this observed increased risk might not be due to unrecognized paroxysmal atrial tachyarrhythmias. Indeed some individuals could have had unidentified atrial tachyarrhythmias. Since this will also be the case for the DCM individuals, we believe this has only limited influence. To further confirm this, the analysis stratified for individuals with or without known atrial tachyarrhythmias did not materially change the results. In the stratum of individuals with atrial tachyarrhythmias the risk of thromboembolic complications was still higher than in those individuals carrying a *LMNA* mutation.

4.2. Prothrombotic phenotype

After further blood analysis in *LMNA* mutation carriers without DCM or atrial tachyarrhythmias, we identified a prothrombotic phenotype. These *LMNA* mutation carriers had, compared with mutation negative relatives, differences in both platelet and hemostatic characteristics.

We found that *LMNA* mutation carriers had a significantly reduced platelet number and that both platelets and platelet–monocyte complexes were less sensitive to stimulation in vitro with an agonist. Furthermore, the platelets of these *LMNA* mutation carriers tended to have an increased MPV, which itself is an independent predictor of ischemic stroke and cardiovascular disease because larger platelets are metabolically and enzymatically more active and are prothrombotic [21,22]. This may reflect mild ongoing platelet activation in vivo [23] since activated platelets in vivo will lose their P-selectin, either by losing P-selectin on the surface or by binding to surface-exposed P-selectin monocytes [24,25]. Because of the in vivo activation, the expression of P-selectin after stimulation with an agonist will be reduced in vitro.

Concerning the hemostatic characteristics, a similar phenomenon was observed. The coagulation system (prothrombin fragment $1+2$) was not activated at baseline. The hemostatic characteristics became more apparent after stimulation. *LMNA* mutation carriers produced more thrombin, which is consistent with the observed clinical phenotype with a high prevalence of thromboembolic complications [26,27].

When combining the results of the platelet and hemostatic characteristics, it suggests that the blood of *LMNA* mutation carriers becomes more thrombotic after in vivo stimulation.

4.3. Relation between LMNA mutation and thromboembolic complications

Lamins A and C are major components of the nuclear lamina. The functions of lamins A and C are not completely understood. It is known that they are important in maintaining the nuclear architecture, DNA replication and cell cycle regulation [1,28]. One possible explanation for the observed prothrombotic phenotype might be the direct influence of the altered lamin A/C protein on the platelets. In fact, instability of the actin structures, as a result of a *LMNA* mutation, could influence fragmentation of platelets from megakaryocytes resulting in an altered platelet production/function or could influence the function of the platelets themselves [29–32]. On the other hand, one might speculate that the prothrombotic phenotype is a result of the influence of the altered lamin A/C protein in the endothelial and/or smooth muscle cells of the vessel wall, hereby influencing the function of the platelets. It might be of additional value to analyze whether there is a relation between the location or type of mutation in *LMNA* and the prothrombotic phenotype, however the number of *LMNA* mutation carriers is too modest in this study.

4.4. Study limitations

The first part of the study was based on the data of two retrospectively collected cohorts, which are sensitive for biases due to the absence of diagnostic and treatment protocols. Therefore, patients might have been treated differently; including different criteria might have been used to start anticoagulant or antiplatelet therapy. We tried to avoid this bias by analyzing only the time-period in which the individuals did not receive anticoagulant and/or antiplatelet therapy.

Concerning the case–control study, we selected a young cohort of individuals without cardiac disease yet and without anticoagulant and/or antiplatelet therapy. We are aware that the exclusion of these individuals could also have given an underestimation of the effect of the *LMNA* mutation on the platelet and hemostatic characteristics.

5. Conclusion

Our results show that carrying a *LMNA* mutation is independently associated with an increased risk of both arterial and venous thromboembolic complications and opens important new avenues for a possible role of anticoagulant and/or antiplatelet therapy as appropriate preventive intervention. In our view, physicians who are treating *LMNA* mutation carriers need to be aware of the prothrombotic phenotype of these individuals.

Funding

This study has been supported by the Netherlands Foundation for Cardiovascular Excellence.

Acknowledgments

We would like to thank all individuals that were willing to cooperate in the study. We are indebted to the assistance of Jan D.H. Jongbloed, Karin Y. van Spaendonck-Zwarts, and Karin Berkenbosch, University Medical Center Groningen, The Netherlands, and Harry R. Büller and Nynke Hofman, Academic Medical Center, Amsterdam, The Netherlands. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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