

厚生労働科学研究費補助金

難治性疾患等政策研究事業（難治性疾患政策研究事業）

成人例の左室緻密化障害の全国調査

平成27年度 総括・分担研究報告書

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平成28（2016）年 5月

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厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）  
（総括・分担）研究報告書

成人例の左室緻密化障害の全国調査

池田 宇一

研究要旨

わが国における成人例の左室緻密化障害の実態を明らかにするために、甲信地区の心エコー検査室における前向きコホート研究および日本心不全学会会員を対象とした後向きコホート研究を開始した。

研究分担者：磯部光章・東京医科歯科大学医学部医学科・循環器制御学(東京医科歯科大学)・教授  
小山 潤・信州大学学術研究院医学系・准教授

A. 研究目的

左室緻密化障害（LVNC; left ventricular non-compaction）はこれまで見過ごされてきた希少心筋疾患で、従来は小児の疾患と考えられてきたが、最近では成人例での報告が散見される。左室緻密化障害は、突然死、心不全、塞栓症などの合併頻度が高いことが報告されているが、わが国における成人例の実態は全く不明である。

成人例の左室緻密化障害の一定の診断基準はまだないが、一般的には断層心エコーまたはMRI検査にて左室内面の肉柱形成とその間の深い陥凹を証明することで診断されている。Jenniは、断層心エコーによる診断基準として「左室が心膜側の緻密化層と心内膜側の非緻密化層の2層からなり、非緻密化層は肉柱様構造で、非緻密化層の厚さが緻密化層の2倍以上」であれば左室緻密化障害と診断できると提唱している(Heart, 2001)。Petersenは、MRIシネ画像で「左室の非緻密化層の厚さが緻密化層の2.3倍以上」であれば左室緻密化障害と診断できるとしている(JACC, 2005)。

成人における左室緻密化障害の発症頻度は不明である。また、左室緻密化障害の予後についても不明な点が多い。Oechslinらの研究が最も大人数で、左室緻密化障害患者34名を平均44ヵ月フォローし、53%が心不全、41%が心室頻拍、24%

が血栓塞栓イベントを発症したと報告しているが(JACC, 2000) わが国のデータは皆無である。このように、希少難治性心筋症である左室緻密化障害の成人例のわが国における発症頻度や予後について明らかでなく、実態は不明である。そこで日本心不全学会では、申請者が委員長を務めるガイドライン委員会が中心となり、多施設コホート研究を実施し、わが国における成人例の左室緻密化障害の発症頻度および予後について明らかにする。

B. 研究方法

【前向きコホート研究】

研究代表者・分担者が所属する施設の心エコー検査室ならびに長野・山梨の両県の基幹病院の心エコー検査室にて検査を受ける患者（年間約50,000名）を対象とする。既に平成27年7月から、研究分担者（小山）が代表を務める甲信心エコー図セミナー会員所属施設において調査を開始している。

【後向きコホート研究】

左室緻密化障害は希少疾患であるため、前向きコホート研究のみでは十分なデータを集積できない可能性がある。そこで、日本心不全学会会員（会員数2,443名）に対してアンケートを送付し、後向きコホート研究を併せて実施する。既に平成27年7月末に日本心不全学会会員にアンケートを送付し、8月中旬時点で約300名の会員から回答を

得ている。

#### (倫理面への配慮)

本調査は信州大学医学部医倫理委員会の承認を得ている。個人情報および試料等は、各施設で連結可能な匿名化したうえで、研究に使用する。家族内発症例には家族のスクリーニングも含め倫理面の十分な配慮を行う。匿名化の対応表およびデータは、同意書とともに鍵のかかるキャビネットに保管する。

#### C. 研究結果

【前向きコホート研究】研究代表者・分担者が所属する施設の心エコー検査室ならびに長野・山梨の両県の基幹病院の心エコー検査室（20施設）にて検査を受ける患者（年間約50,000名）を対象とする。既に平成27年7月に甲信心エコー図セミナー会員所属20施設に調査依頼を行い、前向きコホート研究を開始している。これまでに新規に5名の成人例の左室緻密化障害症例が登録されており、定期的にホルター心電図検査、心エコー検査、血液検査（BNPなど心不全関連マーカー）を実施し、心不全、不整脈、血栓塞栓症イベントの発生について追跡中である。

【後向きコホート研究】平成27年7月に日本心不全学会会員（会員数2,443名）に対して、成人例左室緻密化障害の一次調査のアンケートを送付した。これまでに144名の会員から過去3年以内に成人例左室緻密化障害の症例を経験したとの報告を受けている。現在、これら会員に対して、症例の詳細に関する二次調査を依頼中である。

尚、これら前向きおよび後ろ向きコホート研究の中間結果を、日本心不全学会の分科会である第2回日本心筋症研究会（平成28年5月14日開催）で報告予定である。

#### D. 考察

平成27年度に、成人例の左室緻密化障害の前向きおよび後向きコホート研究に着手した。平成28年度は追跡調査を行い、成人例左室緻密化障害の実態を明らかにする。

#### E. 結論

わが国における成人例の左室緻密化障害の実態調査のため、前向きおよび後ろ向きコホート研究を開始した。

#### F. 健康危険情報

なし

#### G. 研究発表

##### 1. 論文発表

1. Minamisawa M, Koyama J\*, Kozuka A, Miura T, Ebisawa S, Motoki H, Okada A, Iizawa A, Ikeda U. Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy. J Cardiol 2016,(in press)

##### 2. 学会発表

なし

#### H. 知的財産権の出願・登録状況

なし

2015年7月吉日

日本心不全学会会員各位

一般社団法人 日本心不全学会

理事長 磯部光章

ガイドライン委員会委員長 池田宇一

### 「成人例の左室緻密化障害の全国調査」について（ご依頼）

拝啓 初夏の候、会員の皆様におかれましてはますますご清祥のこととお喜び申し上げます。平素より当会の活動に格別のご配慮を賜り、厚く御礼申し上げます。

さて、左室緻密化障害（LVNC; left ventricular non-compaction）はこれまで見過ごされてきた希少心筋疾患で、従来は小児の疾患と考えられてきましたが、最近では成人例での報告が散見されます。LVNCは、突然死、心不全、塞栓症などの合併頻度が高いことが報告されていますが、わが国における成人例の実態は全く不明です。

そこで日本心不全学会では、成人例のLVNCの全国調査を行い、診療ガイドラインの作成の必要性等について検討することになりました。過去3年間(2012年1月～2015年6月)に症例を経験された会員におかれましては、ご多忙のところ恐れ入りますが、同封のアンケート用紙にご記入いただき、2015年7月30日までにご返送くださいますようお願い申し上げます。LVNCの診断については、添付の資料をご参照ください。

なお、本調査は信州大学医学部の倫理委員会の承認を得ていますが、「疫学研究に関する倫理指針」に従い、貴施設の倫理委員会の承認ならびに対象者からインフォームド・コンセントを得る必要はありません。該当する患者情報に関しては後日詳細をお伺い致しますが、これにつきましてもご協力を賜りますようお願い申し上げます。

敬白

本調査に関する問い合わせ先

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**第一次調査アンケート用紙**

成人例の左室緻密化障害の全国調査

所属施設名：\_\_\_\_\_

診療科：\_\_\_\_\_

記載者氏名：\_\_\_\_\_

1) 過去3年間（2012年1月～2015年6月）に、貴施設で成人の左室緻密化障害患者を診療されたことがありますか？

あり ・ なし（いずれかに○をつけて下さい）

「あり」と回答された方のみ、2)以降へお進み下さい。

2) 何症例をご経験されましたか？

\_\_\_\_\_ 症例

小児期より診断されていた症例は除外して下さい。  
下記の疾患としてフォローされていることが報告されています。  
拡張型心筋症、肥大型心筋症、心サルコイドーシス、  
心筋炎、大動脈弁逆流症など。

3) 診断や治療上、問題点がありましたらご自由にご記入下さい。

誠に恐れ入りますが 2015年7月30日までにご返送下さい。

該当症例がない場合も「なし」に○をつけてご返送下さい。

LVNCの診断は添付資料【成人例の左室緻密化障害の暫定診断基準】  
をご参照下さい。

## 【成人例の左室緻密化障害の暫定診断基準】

左室緻密化障害 (LVNC; left ventricular non-compaction) の診断基準として統一されたものではありませんが、一般的には断層心エコー図法または心臓 MRI 検査にて左室内面の肉柱形成と深い間隙を証明することで診断されています<sup>1)</sup>。心エコー図法では Jenni<sup>2)</sup>の基準が最も引用されていますが、他に Chin<sup>3)</sup>が提唱する診断基準などもあります。本調査では Jenni あるいは Chin の診断基準を満たしていれば、LVNC と診断いたします。

### Jenni の診断基準 (図 A)

- 1) 左室心筋が緻密化層(C)と非緻密化層(NC)の2層からなる。
- 2) 収縮末期に NC が C の2倍以上 ( $NC/C > 2$ )。
- 3) カラー Doppler 法で、肉柱の間隙に血流が観察される。
- 4) 他の心臓構造異常を伴わない。

### Chin の診断基準 (図 B)

- 1) 左室心尖部において、肉柱を除いた壁厚(緻密化層)(X)と肉柱を含めた壁厚(非緻密化層+緻密化層)(Y)を求める。
- 2) 拡張末期に  $X/Y \leq 0.5$ 。



図 A: Jenni の基準 (収縮末期)

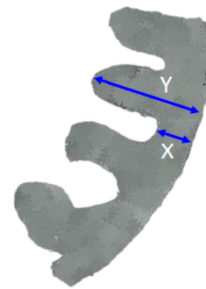


図 B: Chin の基準 (拡張末期)

### 参考文献

- 1) Ikeda U, et al. J Cardiol 2015; 65: 91-97.
- 2) Jenni R, et al. Heart 2001; 86: 666-671.
- 3) Chin TK, et al. Circulation 1990; 82: 507-513

2015年10月吉日

日本心不全学会会員各位

一般社団法人 日本心不全学会

理事長 磯部光章

ガイドライン委員会委員長 池田宇一

### 「成人例の左室緻密化障害の二次調査」について（ご依頼）

拝啓 初秋の候、会員の皆様におかれましてはますますご清祥のこととお喜び申し上げます。平素より当会の活動に格別のご配慮を賜り、厚く御礼申し上げます。

さて、過日、日本心不全学会では、成人例の左室緻密化障害の経験症例について全国一次調査を行い、先生を含む142名の会員の皆様から経験例のご報告をいただきました。

そこで、二次調査として、症例の詳細をお伺い致したく、再度ご協力を賜りますようお願い申し上げます。お忙しいところ大変恐縮ですが、同封の調査票にご記入の上、11月末までに返信用封筒にて事務局までお送りください。

なお、本調査は信州大学医学部の倫理委員会の承認を得ており、「疫学研究に関する倫理指針」に従い、貴施設の倫理委員会の承認ならびに対象者からインフォームド・コンセントを得る必要がないことを申し添えます。

敬白

本調査に関する問い合わせ先

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## 成人例の左室緻密化障害の全国二次調査

所属施設名：

診療科：

ご芳名：

- 
- 1) 先生より、全国一次調査にて【                      例】の経験例をご報告頂きました。各症例につき、別紙個人登録票にご記入をお願い申し上げます。
  - 2) 心エコーデータは、初診時(または一番古いデータ)と直近フォロー時の画像・心エコーレポートもご同封ください。
  - 3) 心エコー画像フォーマットはDVDに記録の上、各 Vendor format (GE, Philips, Toshiba, Aloka)でお送りください。  
(コアラボに Vendor の解析装置がない場合は、AVI, DICOM format での再送付をお願いする場合があります。)
  - 4) お送りいただいたファイルに相当する未使用のDVDを、後日、事務局よりお送り致します。なお、ご送付いただいたファイルは返却いたしませんので、予めご了承ください。

2015年11月末日までに、個人登録票と心エコーデータ(DVDおよび心エコーレポート)を、同封の返信用封筒(レターパック)にて事務局までお送り下さい。

## 【成人例の左室緻密化障害の暫定的診断基準と断層心エコー図所見】

はじめに：左室緻密化障害(LVNC; left ventricular non-compaction)の確立した診断基準は、国内・国外問わず存在していないのが現状であるが、一般的には断層心エコー図法または心臓 MRI 検査にて左室内面の肉柱形成とその間の深い陥凹を証明することで診断されている<sup>a)</sup>。心エコー法では Jenni<sup>b)</sup>らの基準が最も引用されており、他に Chin<sup>c)</sup>、Stollberger<sup>d)</sup>らが提唱する心エコー法による診断基準もある。本調査では **Jenni と Chin らの断層心エコー法による診断基準のうち少なくとも1つ満たしていれば、LVNC と暫定的に診断する。**

### 【1】 Jenni の診断基準<sup>b)</sup>

- 1) 左室心筋が緻密化層(C)と非緻密化層(NC)の2層からなる。
- 2) **収縮末期**に(NC)の壁厚が(C)の2倍以上  $(NC)/(C)>2$  (図 A 参照)
- 3) カラー Doppler 法で、網目状の肉柱形成の陥凹に左室内血流が観察される。
- 4) 他の心臓構造異常を伴わない。

### 【2】 Chin の診断基準<sup>c)</sup>

- 1) 左室心尖部において肉柱部分(非緻密化層)を除いた壁厚(X)と肉柱部分を含めた壁厚(非緻密化層+緻密化層)(Y)を認める。
- 2) **拡張末期**に  $(X)/(Y)\leq 0.5$  (図 B 参照)

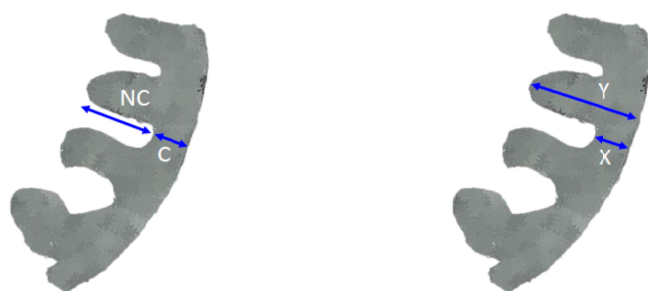


図 A: Jenni の基準(収縮末期)

図 B: Chin の基準(拡張末期)

### 参考文献

- a) Ikeda U, et al. J Cardiol 2015; 65: 91-97.
- b) Jenni R, et al. Heart 2001; 86: 666-671.
- c) Chin TK, et al. Circulation 1990; 82: 507-513
- d) Stollberger C, et al. Am J Cardiol 2002; 90: 899-902

所属施設名、診療科： \_\_\_\_\_

記載者氏名： \_\_\_\_\_

生年月日：西暦 \_\_\_\_\_ 年 \_\_\_\_\_ 月 \_\_\_\_\_ 日、性別： 男性・女性

## 1)【心エコーデータ】

初診時心エコー \_\_\_\_\_ 年 \_\_\_\_\_ 月 \_\_\_\_\_ 日、左室駆出率： \_\_\_\_\_ (%)

直近の心エコー \_\_\_\_\_ 年 \_\_\_\_\_ 月 \_\_\_\_\_ 日、左室駆出率： \_\_\_\_\_ (%)

心エコー画像フォーマット(初診時、直近)は、各 Vender format (GE, Philips, Toshiba, Aloka) で DVD データをお送りください。

初診時、直近の心エコーレポートもご同封ください。

## 2)【初診時データ】

初診日(西暦)： \_\_\_\_\_ 年 \_\_\_\_\_ 月、初診時 NYHA \_\_\_\_\_ . . .

初診時現症 身長： \_\_\_\_\_ cm、体重： \_\_\_\_\_ kg、収縮期/拡張期血圧： \_\_\_\_\_ / \_\_\_\_\_ mmHg

診断基準 Jenni 該当：なし、あり Chin 該当：なし、あり

基礎心疾患 基礎心疾患なし・先天性心疾患( \_\_\_\_\_ )・拡張型心筋症・肥大型心筋症・弁膜症・  
虚血性心筋症・二次性心筋症(心サルコイドーシス・神経筋疾患・その他： \_\_\_\_\_ )・

## 初診時点での既往症

心不全入院歴(なし、あり)、不整脈入院歴(なし、あり)、血栓塞栓症入院歴(なし、あり)

高血圧(なし、あり)、糖尿病(なし、あり)、心房細動(なし、あり)、心室頻拍(なし、あり)

LVNC の家族歴(なし、あり)

初診時点での内服薬 抗血小板薬(なし、あり)・抗凝固薬(なし、あり)・ACE-I(なし、あり)・

ARB(なし、あり)・Blocker(なし、あり)・アルドステロン拮抗薬(なし、あり)・ループ利尿薬(なし、あり)

## 初診時 血液検査

BNP (pg/mL)	NT-proBNP (pg/mL)	Hb (g/dL)	Alb (g/dL)
Cr (mg/dL)	eGFR (mL/min/1.73m <sup>2</sup> )	Na (mEq/L)	

## 他検査の有無

冠動脈造影検査 (未施行)・(施行済：0枝、1枝、多枝)

心筋生検 (未施行)・(施行済：所見 \_\_\_\_\_ )

ホルター心電図 (未施行)・(施行済：総心拍数 \_\_\_\_\_ 、非持続性心室頻拍あり、持続性心室頻拍あり)

心臓 MRI 検査 (未施行)・(施行済：遅延造影 \_\_\_\_\_ 陰性・陽性)

### 3)【フォロー時データ】

最終観察日(西暦)： \_\_\_\_\_ 年 \_\_\_\_\_ 月、 最終観察時 NYHA . . .

#### 初診後のイベント発症の有無

フォロー (不明、あり)  
死亡 (なし、あり：発症日 原因：心不全死、不整脈死、非心臓死)  
心不全入院歴 (なし、あり：初回発症日 )  
不整脈入院歴 (なし、あり：初回発症日 )  
血栓塞栓症入院歴 (なし、あり：初回発症日 )

#### 初診後の治療有無

フォロー (不明、あり)  
ICD (なし、あり：施行日 )  
CRT (なし、あり：施行日 )  
心移植 (なし、あり：施行日 )  
体内(外)式植込み型人工補助心臓 (なし、あり：施行日 )

### 4)【自由記述】

診断、治療上、問題事項がありましたらご自由にご記入下さい。

LVNC の診断は添付資料【成人例の左室緻密化障害の暫定診断基準】をご参照下さい。  
誠に恐れ入りますが、2015年11月末日までにご返送下さい。

厚生労働科学研究費補助金（難治政策 三次公募採択課題）  
（分担）研究報告書

成人例の左室緻密化障害の後ろ向き観察研究

研究分担者 磯部光章 東京医科歯科大学大学院医歯学総合研究科循環制御内科学

研究要旨：かつては、左室緻密化障害は心筋の構築異常を伴う先天性心筋疾患であり、主に小児循環器科にて診療される疾患と考えられていたが、近年、小児のみならず成人例での報告例が増加している。現状では確立していない左室緻密化障害の診断基準を制定するためには左室緻密化障害の患者の実態調査を行う必要があるが、左室緻密化障害は希少疾患であるため、前向き観察研究のみでは十分なデータを収集できない可能性を考慮し、後ろ向き観察研究を施行することとした。

A．研究目的

希少難治性疾患であるが、確立した診断基準がない左室緻密化障害の患者の実態を明らかにすること。

B．研究方法

当施設における2001年からの入退院患者のデータベースを検索し、成人左室緻密化障害の症例をピックアップする。このうち、今回の研究の対象である「2012年1月～2015年6日までの期間に当院および共同研究機関において心エコー検査室にて検査を受けた患者」に該当する症例を探索し、その症例の病歴、諸検査の所見、心エコー検査の画像データを得る。

C．研究結果

当施設における2001年からの入退院患者のデータベースを検索したところ、3例の成人左室緻密化障害の症例が見いだされた。このうち、今回の研究の対象である「2012年1月～2015年6日までの期間に当院および共同研究機関において心エコー検査室にて検査を受けた患者」に合致する症例は1例であった。この患者の病歴、諸検査の所見、心エコー検査の画像データを主研究機関である信州大学医学部附属病院循環器内科に送付することで、本研究のデータ解析に寄与した。

（倫理面への配慮）

本研究は診療録をもとにした観察研究であるため、疫学研究の倫理指針(第3項1-(2)-イ)に基づき、患者本人からのインフォームド・コンセント取得は必要としない。しかし、研究計画に関しては院内掲示やホームページにて公表し、研究対象者とな

る患者が研究参加を拒否できるように十分配慮している。いずれの段階でも拒否でき、拒否による不利益はないものとする。このように、本研究を遂行するにあたり、倫理面で十分な配慮がなされているものとする。

D．考察

今回当施設にて当該疾患の後ろ向き調査を行ったが、希少疾患である成人左室緻密化障害症例の収集は非常に困難であることを改めて実感した。このことを踏まえ、今後はより多くの施設に参加を呼びかけていく必要があると考える。

E．結論

成人左室緻密化障害の症例の収集を単施設にて行った。今後は一次、二次調査を経て得られた左室緻密化障害の症例に関するデータを主研究機関にてまとめて患者の実態を明らかにし、この結果を左室緻密化障害の診断基準を確立するための基礎データとするため本研究を引き続き行っていく方針とした。

F．健康危険情報：省略

G．研究発表

1. 論文発表：なし
2. 学会発表：なし

H．知的財産権の出願・登録状況

1. 特許取得：なし
2. 実用新案登録：なし
3. その他：なし

厚生労働科学研究費補助金（難治性疾患等政策研究事業(難治性疾患政策研究事業)）  
（分担）研究報告書

成人例の左室緻密化障害の全国調査

小山 潤

研究要旨：近年、心臓超音波検査装置の技術革新により、左室心筋の緻密化障害症例が散見されるようになった。本研究は、左室緻密化障害を呈する患者の特徴、並存心疾患の種類、治療による形態の変化、リモデリングとの関連を全国調査により明らかにすることである。また、前向きに心臓超音波検査により患者を登録し、治療による臨床経過を観察することである。

A．研究目的

近年、心臓超音波検査装置の進歩により、左室緻密化障害を呈する患者を散見するようになった。疾患概念としては、胎生期の左室緻密化が停止することで生ずる異常とされるが、成人例でこのような形態を呈する患者が多く報告されており、ガイドライン上も統一された見解はない。本研究は、比較的疾患頻度が稀な左室緻密化障害の全国調査を行うことで、本疾患の頻度、並存する心疾患の種類、臨床経過などを明らかにし、ガイドライン作成を行うことである。

B．研究方法

日本心不全学会に属する会員向けに、アンケート調査を行い、本疾患の並存疾患、治療による形態の変化の有無などを明らかにする。また、同症例の心エコー画像を匿名化した上で提供してもらい、形態的な特徴の計測をコアラボラトリーで行い、形態学的な特徴を明らかにし、形態学的診断基準をリニューアルする。  
また、前向きに患者登録を行い、治療による臨床経過の観察、リモデリングに伴う形態の変化の有無を明らかにする。

（倫理面への配慮）

信州大学倫理委員会の承認を得ている。また、匿名化画像の供出に関し、必要に応じて施設ごとに倫理委員会に諮り承認を得ている。

C．研究結果

全国調査の結果500名前後の症例が報告された。疾患の背景因子、並存疾患の種類、治療後の形態の変化などを集計中である。

D．考察

少数患者の前向き試験では、左室のリバースリモデリングに伴い、左室緻密化障害の形態が消失する傾向にあり、本形態は左室容量負荷に伴い出現する可能性がある。全国調査の結果も本知見を裏付ける結果となることが期待される。

E．結論

成人における左室緻密化障害は、先天的な異常ではなく、左室容量負荷を呈するような病態により出現する可能性が高い。

F．健康危険情報

なし

G．研究発表

1. 論文発表

1. Minamisawa M, Koyama J\*, Kozuka A, Miura T, Ebisawa S, Motoki H, Okada A, Iizawa A, Ikeda U. Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy. J Cardiol 2016,(in press)

2. 学会発表

なし

H．知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Minamisawa M, Koyama J*, Kozuka A, Miura T, Ebisawa S, Motoki H, Okada A, Izawa A, Ikeda U.	Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy.	J Cardiol	in press		2016



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Original article

## Regression of left ventricular hypertrabeculation is associated with improvement in systolic function and favorable prognosis in adult patients with non-ischemic cardiomyopathy

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### ABSTRACT

**Background:** We sometimes experience regression of left ventricular hypertrabeculation (LVHT), which is compatible with the diagnosis of LV non-compaction cardiomyopathy (LVNC) in adult patients. However, little is known about the association between LVHT regression and LV systolic function in adult patients.

**Methods:** We prospectively examined 23 consecutive adult patients who fulfilled the echocardiographic criteria for LVNC. LV reverse remodeling (RR) was defined as an absolute increase in LV ejection fraction of > 10% at 6 months follow-up. LVHT area was calculated by subtraction from the outer edge to the inner edge of the LVHT at end-systole.

**Results:** The mean follow-up period was 61 months. LVRR was observed in 9 patients (39%). The changes in the mean LVHT area showed significant correlation with the changes in LV ejection fraction ( $r = -0.78$ ,  $p < 0.0001$ ). Cardiac death occurred in 7 patients (50%) without LVRR, but no patients with LVRR died (log-rank,  $p = 0.003$ ). Furthermore, composite of cardiac death and hospitalization for heart failure occurred in 10 patients (71%) without LVRR, whereas there was one patient with LVRR (log-rank,  $p < 0.001$ ).

**Conclusions:** Regression of LVHT is associated with improvement in LV systolic function. LVRR might be associated with a favorable prognosis in patients with LVHT.

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Left ventricular (LV) non-compaction cardiomyopathy (LVNC) is a rare, congenital heart disease characterized by LV hypertrabeculation (LVHT), which is thought to be the result of a failure of trabecular regression during normal embryonic development [1–4]. LVNC is usually associated with LV systolic dysfunction, an increased incidence of thromboembolism, and ventricular arrhythmia [4,5].

Previous reports in adults indicated that LV systolic dysfunction that fulfilled the echocardiographic criteria for LVNC sometimes showed regression of LVHT and LV reverse remodeling (LVRR) after optimal therapy [6–9]. However, little is known about the

relationship between the regression of LVHT and LVRR in adult patients with LVHT, which may be compatible with the diagnosis of LVNC. The aim of this study was to clarify the relationship between the regression of LVHT and LVRR.

### Methods

#### Study population

This study was a prospective observational study conducted between December 2005 and December 2014 in a single center. We included all consecutive patients who were referred to our department with non-ischemic LV systolic dysfunction and an LV ejection fraction (LVEF) < 40%. There were 300 patients with LV systolic dysfunction during the period. All patients had undergone coronary angiography, and had no significant coronary artery disease, defined as > 50% diameter narrowing in any of the major

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coronary arteries. Among them, we found 23 consecutive adult patients (7.7%) who fulfilled Jenni's echocardiographic criteria for LVNC in our study [10]. These criteria are based on a double-layered appearance of the LV myocardium on two-dimensional (2D) echocardiography. Patients with LVHT, which may be compatible with the diagnosis of LVNC, are defined as having a ratio of non-compacted layer to compacted layer (NC/C) in the LV myocardium of more than double, measured at end-systole in a parasternal short-axis view. Patients with a history of other congenital, acquired, or significant valvular heart disease, or neuro-muscular disease [11] were excluded from our study. No patients showed inflammatory findings, such as cardiac sarcoidosis and endomyocarditis, on the basis of the endomyocardial biopsy from the right ventricle ( $n = 20$ ), gallium scintigraphy ( $n = 3$ ), and past history from the medical records at baseline. The institutional review board approved the protocol, and written informed consent was obtained from each patient before the ultrasound examination.

#### Ultrasound examination and measurement

All ultrasound examinations were performed using a commercially available echocardiographic machine with an S3 transducer (Vivid Seven System, GE Healthcare, Horten, Norway). Parasternal and apical projections were obtained according to the recommendations of the American Society of Echocardiography [12,13]. The left atrial diameter was determined from the M-mode recording as the largest distance between the posterior aortic wall and the posterior left atrial wall at end-systole. The thicknesses of the interventricular septum and LV posterior wall and the LV end-diastolic and end-systolic diameters were determined from the M-mode recording at the level of the chordae. The LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF were calculated using biplane Simpson's methods from apical four- and two-chamber views. Pulsed Doppler echocardiographic measurements of the transmitral and pulmonary venous flow velocities were obtained by positioning the sample volume at the level of the mitral tips and 1 cm below the ostium of the right upper pulmonary vein, respectively. The off-line analysis of transmitral flow and pulmonary venous flow was performed with the use of dedicated software (EchoPAC Version 112, GE Healthcare). Three consecutive beats were measured and averaged for each measurement during sinus rhythm. In atrial fibrillation rhythm, an index beat, a beat following two preceding intervals that were nearly the same, was used for each measurement [14,15]. The peak velocities of early (E) and late filling (A) waves, the E/A ratio of peak velocities, and the deceleration time (DT) of the E-wave were measured from transmitral flow velocities, and the peak velocities of systolic (S), diastolic (D), and A waves, together with the S/D ratio of peak velocities, were also measured from the pulmonary venous flow velocities. The early diastolic mitral annular velocity of the septal and lateral mitral annulus ( $e^0$  velocity) was obtained by tissue Doppler imaging and the E/ $e^0$  ratio was calculated. The location of LVHT was assessed and categorized as apical if it involved the LV apex and as anterior, lateral, or posterior if it involved the anterior, lateral, or posterior in each LV segment from the three apical views [16]. With respect to 2D speckle-tracking echocardiography, the second-harmonic B-mode images were obtained for offline analysis (EchoPAC Version 112). Apical four- and two-chamber, and long-axis views were used for the measurements of LV longitudinal strain. The LV endocardial border of the inner edge of the compacted layer was manually traced on the end-systolic frame, and the software subsequently and automatically traced the borders in the other frames. LV global longitudinal strain (GLS) was calculated as the mean longitudinal peak

negative strain from each of three apical views during a cardiac cycle [17].

#### Clinical and long-term assessment

The study patients were treated with angiotensin-converting enzyme inhibitors and/or angiotensin type 1 receptor blockers and beta-blockers in addition to diuretics according to the guidelines [18]. The indication for cardiac resynchronization therapy was advanced heart failure along with LV diastolic diameter  $>55$  mm, LVEF  $<35\%$ , QRS interval  $>120$  ms, or mechanical dyssynchrony with narrow QRS [19]. LVHT areas were calculated by subtraction from the outer edge of the LVHT area to the inner edge of the LVHT area at end-systole in the three apical views (Fig. 1). LVRR was defined as an absolute increase in LVEF of more than 10% at 6-month follow-up [20].

#### Interobserver and intraobserver variability

The inter- and intraobserver variabilities for LV GLS were studied in a group of 20 randomly selected subjects, using measurements by one observer, repeated twice  $>2$  weeks after the first measurements, and by two observers who were unaware of each other's measurements. The bias (mean difference) and limits of agreement (1.96 standard deviation of difference) between the first and second measurements were determined. To assess reproducibility, the coefficient of variation was calculated as the standard deviation of the difference divided by the mean.

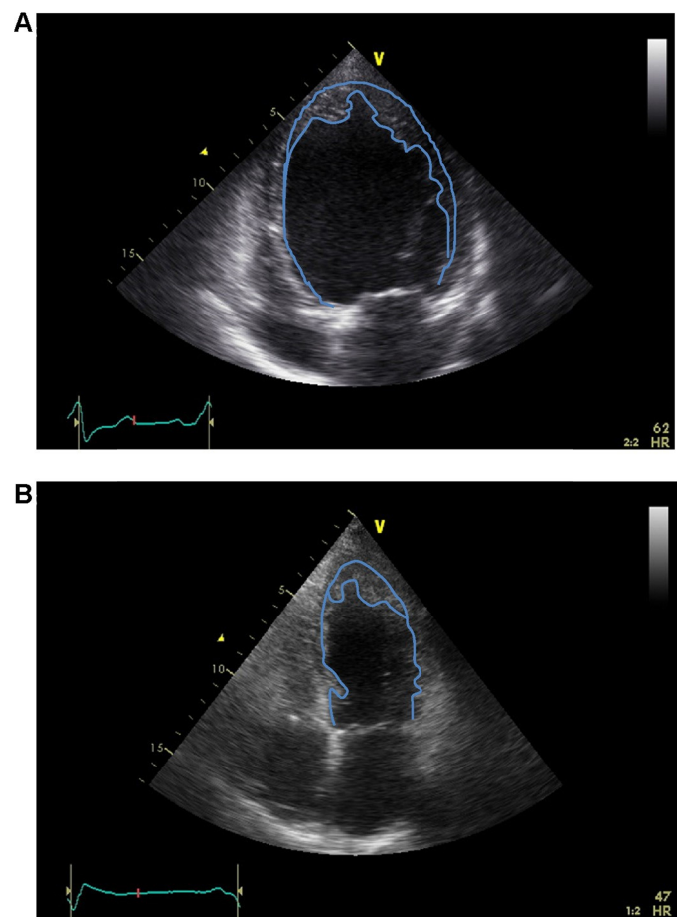


Fig. 1. Representative example of echocardiographic measurement of left ventricular hypertrabeculation area in apical four-chamber view (A) at baseline and (B) at 6 months' follow-up. (LV Hypertrabeculation Area) = (The Outer Edge of LVHT) - (The Inner Edge of LVHT). LVHT, left ventricular hypertrabeculation.

Statistical analyses

Continuous variables were summarized as mean ± standard deviation if normally distributed, and as median and interquartile range otherwise. Normality was evaluated by the Shapiro–Wilk W test. Comparisons of baseline characteristics between patients with and without LVRR were assessed using Student’s t-test and the Mann–Whitney U test for normally and non-normally distributed data, respectively. To elucidate the prolonged influence of LVRR on clinical outcome, Kaplan–Meier curves were calculated from 6 months (the start-point) to the time of cardiac events (cardiac death, mechanical circulatory support, and hospitalization for heart failure) and compared using the log-rank test. A mixed-model repeated-measures analysis of variance was used to compare the two groups from baseline until 24 months. Associations between the regression of LVHT, as estimated by changes in LVHT area, and the changes in LV systolic function were tested using Pearson or Spearman correlation. The optimal receiver-operating characteristic (ROC) curve cut-off value for predicting cardiac events was chosen as the value maximizing sensitivity and specificity. A value of  $p < 0.05$  was considered to indicate statistical significance. All analyses were performed using commercially available software (SPSS, version 21.0; SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics and conventional echocardiography at baseline

No patients are dropped out and all patients completed the follow-up. The clinical characteristics are listed in Table 1. LVRR, defined as an absolute increase in LVEF of more than 10% at 6 months’ follow-up, was observed in 9 patients (39%). Age, hemoglobin level, past history of heart failure hospitalization, and duration of heart failure in patients without LVRR at baseline were significantly higher compared to those in patients with LVRR. As to drug therapies at baseline, the use of angiotensin-converting enzyme inhibitors and/or angiotensin type 1 receptor blockers, beta-blockers, and aldosterone antagonists in patients without LVRR was significantly more frequent compared to those in patients with LVRR. At 6 months’ follow-up, the use of cardiac

resynchronization therapy and aldosterone antagonists in patients without LVRR was significantly more frequent compared to those in patients with LVRR. Conventional 2D echocardiographic features are listed in Table 2. Baseline echocardiographic parameters, such as LVEF, LV GLS, LVHT area, LV area, and the percentage of LVHT area divided by LV area at end-systole in the three apical views did not differ between the two groups at baseline. Furthermore, there was no difference in the location of LVHT, which was most frequently the apex, followed by the lateral wall, between the two groups.

Clinical changes during the follow-up period

Fig. 1 shows the representative example of the regression of LVHT in apical four-chamber view. Fig. 2A shows the changes in the maximum ratio of NC/C in the LV myocardium from baseline to 24 months’ follow-up. There was a significant interaction between the two groups ( $p < 0.001$  for interaction). The maximum NC/C ratio decreased significantly in patients with LVRR compared to baseline values, and this improvement was maintained throughout the remainder of the 24-month term of this study. In patients with LVRR, LVEF at 6 and 12 months’ follow-up showed significant improvement compared to baseline values, whereas the improvement at 24 months was not significantly different to that observed at 6 months ( $p = 0.071$ ). In patients without LVRR, LVEF did not differ significantly during the entire follow-up period (Fig. 2B).

Table 3 summarizes the serial changes in blood pressure, LV morphology, and plasma BNP levels. There were significant interactions between the two groups with regard to LV GLS, LVHT area, LV area, and the percentage of LVHT area ( $p = 0.002, p = 0.002, p < 0.001$ , and  $p < 0.001$  for interaction, respectively). LV GLS, LVHT area, LV area, and the percentage of LVHT area showed significant improvement at 6, 12, and 24 months in patients with LVRR compared to baseline values. In patients without LVRR, LV GLS and LVHT area did not differ significantly during follow-up. Plasma BNP levels were significantly improved at 6, 12, and 24 months in patients with LVRR compared to baseline values, whereas patients without LVRR showed no significant difference in plasma BNP levels during follow-up. The mean follow-up period

Table 1  
Baseline characteristics.

	LVRR present at 6 months (n = 9)	LVRR absent at 6 months (n = 14)	p-Value
Age, years	47 ± 14	60 ± 6	0.028
Male/Female	7/2	9/5	0.16
Heart rate (beats/min)	76 ± 12	71 ± 15	0.14
Systolic pressure (mmHg)	119 ± 23	102 ± 17	0.21
Diastolic pressure (mmHg)	74 ± 12	65 ± 9	0.11
Body mass index (kg/m <sup>2</sup> )	22.1 ± 3.9	21.8 ± 3.3	0.89
NYHA class (I/II/III/IV)	0/3/6/0	0/1/10/3	0.059
Hemoglobin (g/dL)	14.3 ± 1.9	12.6 ± 1.7	0.031
Albumin (g/dL)	4.2 ± 0.4	3.8 ± 0.3	0.057
Creatinine (mg/Dl)	1.2 ± 0.9	1.3 ± 0.4	0.64
BNP (pg/mL)	846 [306, 1017]	617 [231, 1074]	0.86
Atrial fibrillation	4 (44)	6 (43)	0.41
Left bundle branch block	2 (22)	3 (21)	0.56
Past history of heart failure hospitalization	7 (78)	13 (93)	0.046
Duration of heart failure (months)	6 [5, 60]	36 [17, 90]	0.036
Past history of stroke	0	2 (16%)	0.26
Medication, baseline/at 6 months			
ACE-I/ARB	3 (33)/8 (88)	14 (100)/14 (100)	0.001/0.32
Beta blocker	3 (33)/9 (100)	118 (79)/14 (100)	0.030/1.00
Aldosterone antagonist	0 (0)/3 (33)	10 (77)/13 (93)	0.001/0.01
Warfarin	1 (11)/2 (22)	7 (50)/8 (62)	0.04/0.05
CRT-P (D), baseline/at 6 months	0 (0)/4 (44)	2 (14)/10 (71)	0.24/0.025

Data are shown as mean values ± standard deviation, median [25th, 75th percentiles], or n (percentage).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; BNP, brain-type natriuretic peptide; CRT-P(D), cardiac resynchronization therapy pacemaker (defibrillator); LVRR, left ventricular reverse remodeling; NYHA, New York Heart Association.

Table 2  
 Baseline echocardiographic characteristics and Doppler flow data.

	LVRR present at 6 months (n = 9)	LVRR absent at 6 months (n = 14)	p-Value
Left atrial diameter (mm)	43.5 ± 7.3	51.5 ± 9.3	0.14
LV end-diastolic diameter (mm)	75.2 ± 9.9	71.7 ± 10.8	0.48
LV end-systolic diameter (mm)	67.2 ± 8.8	63.0 ± 11.2	0.40
Transmitral flow			
Peak E velocity (m/s)	0.94 ± 0.33	0.95 ± 0.35	0.52
Peak A velocity (m/s)	0.60 ± 0.27	0.59 ± 0.24	0.92
E/A	1.56 ± 1.24	1.61 ± 1.45	0.60
Deceleration time (ms)	145.8 ± 68.6	157.7 ± 63.2	0.59
Pulmonary venous flow			
Peak S-velocity (m/s)	0.28 ± 0.16	0.36 ± 0.18	0.07
Peak D-velocity (m/s)	0.55 ± 0.19	0.57 ± 0.21	0.51
Peak A-velocity (m/s)	0.25 ± 0.09	0.22 ± 0.09	0.35
Mitral annulus TDI			
E/e <sup>0</sup> (septum)	17.7 ± 1.2	19.1 ± 8.8	0.53
E/e <sup>0</sup> (lateral)	13.1 ± 3.5	14.0 ± 7.6	0.58
LV end-diastolic volume (mL)	278 ± 84	247 ± 92	0.43
LV end-systolic volume (mL)	205 ± 67	180 ± 74	0.42
LV ejection fraction (%)	26.2 ± 8.1	28.1 ± 8.7	0.26
LV global longitudinal strain (%)	-7.1 ± 2.5	-6.9 ± 2.3	0.85
Mean values of LV			
hypertrabeculation area in apical three-chamber view (cm <sup>2</sup> )	11.6 ± 3.0	9.6 ± 1.9	0.33
Mean values of LV area in apical three-chamber view (cm <sup>2</sup> )	50.8 ± 10.4	47.6 ± 12.5	0.53
(LV hypertrabeculation area) × 100/LV area (%)	22.9 ± 2.7	20.6 ± 3.4	0.11
LVHT location			
Apex	9 (100)	13 (93)	0.44
Anterior wall	1 (11)	3 (21)	0.55
Lateral wall	7 (78)	14 (100)	0.67
Inferior wall	5 (56)	7 (50)	0.81
Septal wall	1 (11)	3 (21)	0.55

Data are shown as mean values ± standard deviation, median [25th, 75th percentiles], or n (percentage).  
 e<sup>0</sup>, peak early diastolic velocity of the mitral annulus; LV, left ventricle/left ventricular; LVRR, left ventricular reverse remodeling; TDI, tissue Doppler imaging.

was 49.3 months (range 9.6–79.5) in patients without LVRR and 78.8 months (range 42.8–105.3) in patients with LVRR. Patients with LVRR were tracked for longer than patients without LVRR ( $p = 0.004$ ).

Fig. 3 shows the linear correlation between the changes in LVEF/LV GLS and the changes in the mean values of LVHT area calculated from the three apical views from baseline to 6 months' follow-up. Changes in the mean values of LVHT area showed a significant negative and positive correlation with changes in LVEF and LV GLS ( $r = -0.78$  and  $r = 0.61$ ,  $p < 0.001$  and  $p = 0.002$ , respectively). During follow-up, cardiac death occurred in 7 patients (50%) without LVRR, whereas no patients with LVRR died (log-rank,  $p = 0.003$ ) (Fig. 4A). Mechanical circulatory support was used in 3 patients without LVRR, but was not used in patients with LVRR (log-rank,  $p = 0.001$ ) (Fig. 4B). Hospitalization for heart failure occurred in 10 patients (71%) without LVRR, whereas there was 1 patient with LVRR (log-rank,  $p < 0.001$ ) (Fig. 4C). In the Kaplan-Meier curves for cardiac events on the basis of the changes in the degree of LVHT, the patients with the maximum ratio of NC/C in the LV myocardium of smaller than double at 6 months' follow-up (incompatible with Jenni's echocardiographic criteria,  $n = 13$ ) showed significantly better prognoses than did those compatible with the above criteria at the same period ( $n = 10$ ) (Fig. 4D–F).

Predictor of cardiac events

On the basis of the changes in LVHT from baseline to 6 months' follow-up, ROC curves for predicting cardiac events are shown in

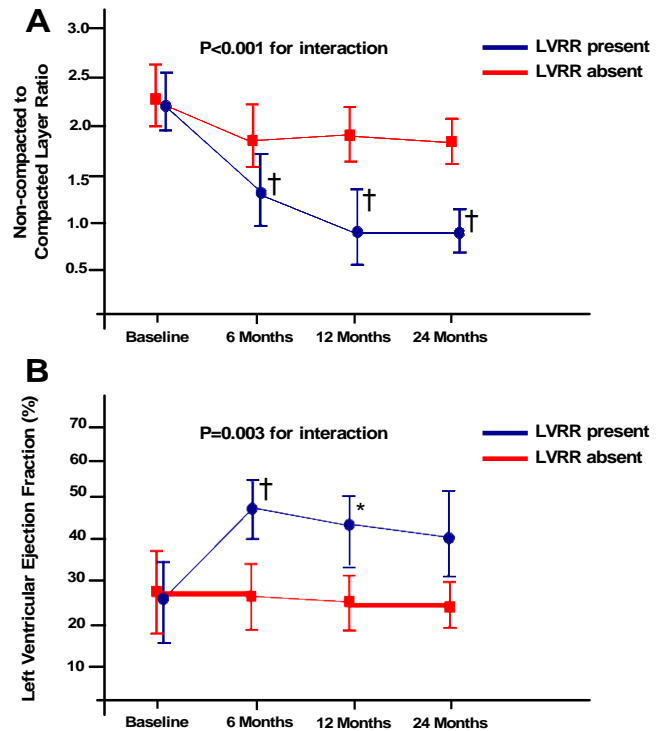


Fig. 2. Changes in (A) the maximum ratio of the non-compacted to the compacted layer in the left ventricular myocardium and (B) left ventricular ejection fraction at baseline, and 6, 12, and 24 months after optimal therapy. \* $p < 0.05$  versus baseline. <sup>y</sup> $p < 0.01$  versus baseline. LVRR, left ventricular reverse remodeling.

Fig. 5. As determined by ROC curve analysis for predicting cardiac death, the regression in the ratio of the NC/C > 0.41 (sensitivity 75.0%, specificity 80.0%) and the regression in the LVHT area > 2.2 cm<sup>2</sup> (sensitivity 87.5%, specificity 74.3%) at 6 months' follow-up predicted the event free from cardiac death.

Reproducibility

The intraobserver coefficient of variation for LV GLS was 7.3% and the interobserver coefficient was 6.3%. The bias and limits of agreement of intra- and interobserver variabilities were  $0.4 ± 2.4%$  and  $0.5 ± 2.0%$ , respectively.

Discussion

To the best of our knowledge, this is the first study to demonstrate the relationship between the regression of LVHT and prognosis. The main findings can be summarized as follows: (1) we described several cases of regression of LVHT in adult patients during the follow-up period, indicating that LVHT might be reversible in some patients; (2) the regression of LVHT, as estimated by a change in LVHT area, showed a significant correlation with the change in LV systolic function, as expressed by LVEF and LV GLS; (3) LVRR in adult patients with the diagnosis of LVNC was observed in 39% (9 cases of 23 patients) and was associated with a better prognosis compared to that in patients without LVRR; and (4) long-term echocardiographic follow-up of cardiac function demonstrated that LVEF and LV GLS in patients with LVRR had improved significantly at 6 months, and this improvement was maintained throughout the remainder of the 24-month term of this study, whereas no such change was seen in patients without LVRR.

Previous reports indicated that LV systolic dysfunction that fulfills the echocardiographic criteria for LVNC sometimes showed



Table 3  
Clinical parameters at baseline, 6, 12, and 24 months (M) after optimal therapy.

	LVRR present at 6 months (n = 9)				LVRR absent at 6 months (n = 14)				Mixed model ANOVA	
	Baseline	6 M	12 M	24 M	Baseline	6 M	12 M	24 M	Time* Group	Group
LVNC appearance (No./No. at risk)	9/9	1/9	1/9	0/7	14/14	9/14	6/11	5/9		
SBP (mmHg)	119 23	119 35	117 31	109 26	102 17	99 20	103 16	99 16	0.71	0.88
DBP (mmHg)	74 12	69 19	71 16	65 13	65 9	65 9	61 11	64 10	0.56	0.68
LVEDV (mL)	278 84	158 52 <sup>y</sup>	163 57 <sup>y</sup>	153 51 <sup>y</sup>	247 92	262 90 <sup>4</sup>	225 85	243 81 <sup>4</sup>	<0.001	0.15
LVESV (mL)	205 67	87 36 <sup>y</sup>	96 50 <sup>y</sup>	98 45 <sup>y</sup>	180 74	194 93	175 52	195 99	<0.001	0.102
LV GLS (%)	-7.1 2.5	-10.7 1.8*	-10.3 2.0*	-10.7 2.9*	-6.9 2.3	-7.2 2.7	-7.1 2.7	-5.8 1.9	0.002	0.035
LVHT area (cm <sup>2</sup> )	11.6 3.0	5.3 2.4 <sup>y</sup>	3.3 1.4 <sup>y</sup>	3.2 0.7 <sup>y</sup>	9.6 1.9	9.8 2.3	8.1 3.2	9.2 3.5	0.003	0.005
LV area (cm <sup>2</sup> )	50.8 10.4	34.6 9.2 <sup>y</sup>	32.7 9.4 <sup>y</sup>	31.6 8.2 <sup>y</sup>	47.6 12.5	46.9 12.2	45.6 12.2	47.8 14.6	0.002	0.005
(LVHT area) 100/LV area (%)	22.9 2.7	15.4 5.5 <sup>y</sup>	9.7 2.2 <sup>y</sup>	10.6 2.7 <sup>y</sup>	20.6 3.4	21.4 3.4	17.5 4.1	19.2 3.4	<0.001	0.055
BNP (pg/mL)	846 [306, 1017]	22 [10, 42] <sup>y</sup>	40 [17, 146] <sup>y</sup>	33 [15, 68] <sup>y</sup>	617 [231, 1074]	424 [246, 655]	301 [203, 687]	368 [171, 552]	0.079	<0.001

Data are shown as mean values ± standard deviation, or median [25th, 75th percentiles].  
 BNP, brain-type natriuretic peptide; DBP, diastolic blood pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVHT, left ventricular hypertrabeculation; LVNC appearance, left ventricular non-compaction cardiomyopathy appearance, i.e. appearance defined as a ratio of non-compacted layer to compacted layer in the left ventricular myocardium of more than double, measured at end-systole in a parasternal short-axis view; LVRR, left ventricular reverse remodeling; SBP, systolic blood pressure.

\* p < 0.05 versus baseline.  
<sup>y</sup> p < 0.01 versus baseline.

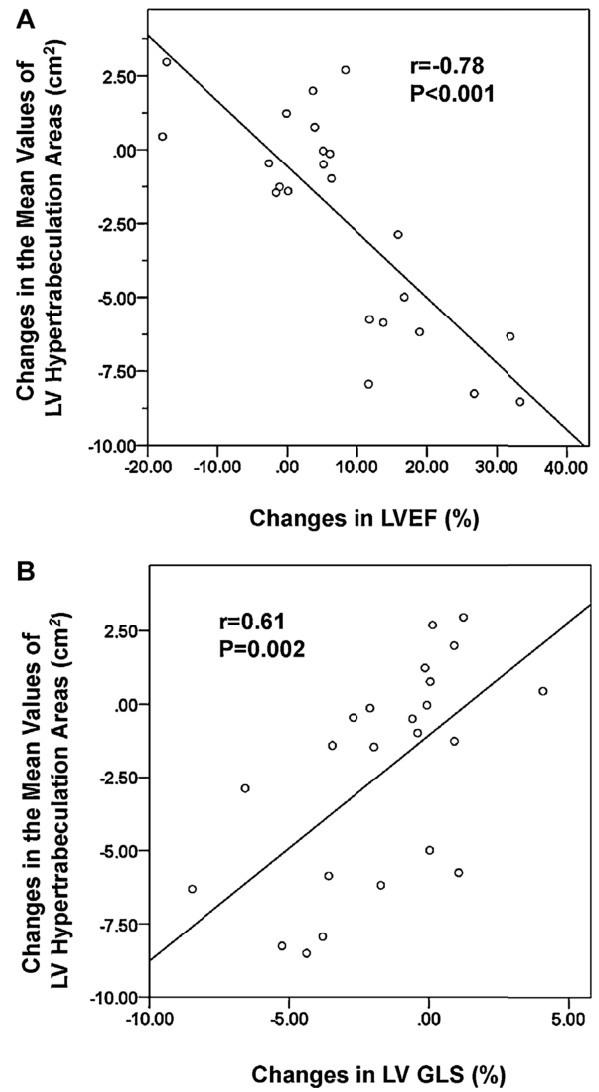


Fig. 3. (A) Linear correlation between changes in left ventricular hypertrabeculation area and changes in left ventricular ejection fraction from baseline to 6 months' follow-up. (B) Linear correlation between changes in left ventricular hypertrabeculation area and changes in left ventricular global longitudinal strain from baseline to 6 months follow-up. LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

regression of LVHT after optimal therapy [6–9]. Stöllberger et al. reported the disappearance of LVHT after biventricular pacing in a patient with polyneuropathy. In this report, LVHT was assumed to represent a compensatory mechanism of the failing myocardium as an attempt to increase the inner myocardial surface and hence the stroke volume. Therefore, improvement in LV systolic function and a decrease in LV size were accompanied by the disappearance of LVHT [7]. This study might indicate that regression of LVHT is associated with an improvement in LV systolic function, as shown in our study. In a study by Gati et al., 102 pregnant women with a morphologically normal LV myocardium at baseline were evaluated longitudinally with echocardiography and 26 (25%) of them developed de novo LVHT during pregnancy. During the post-partum follow-up period of 24 months, 19 (73%) women demonstrated complete resolution of LVHT and 5 showed regression. In some women, de novo LVHT appeared in response to increased LV loading conditions during pregnancy; this phenomenon showed a reversible change after delivery, following normalization of blood volume [21]. The reversible de novo LVHT in this report might partially explain why LVHT is reversible in

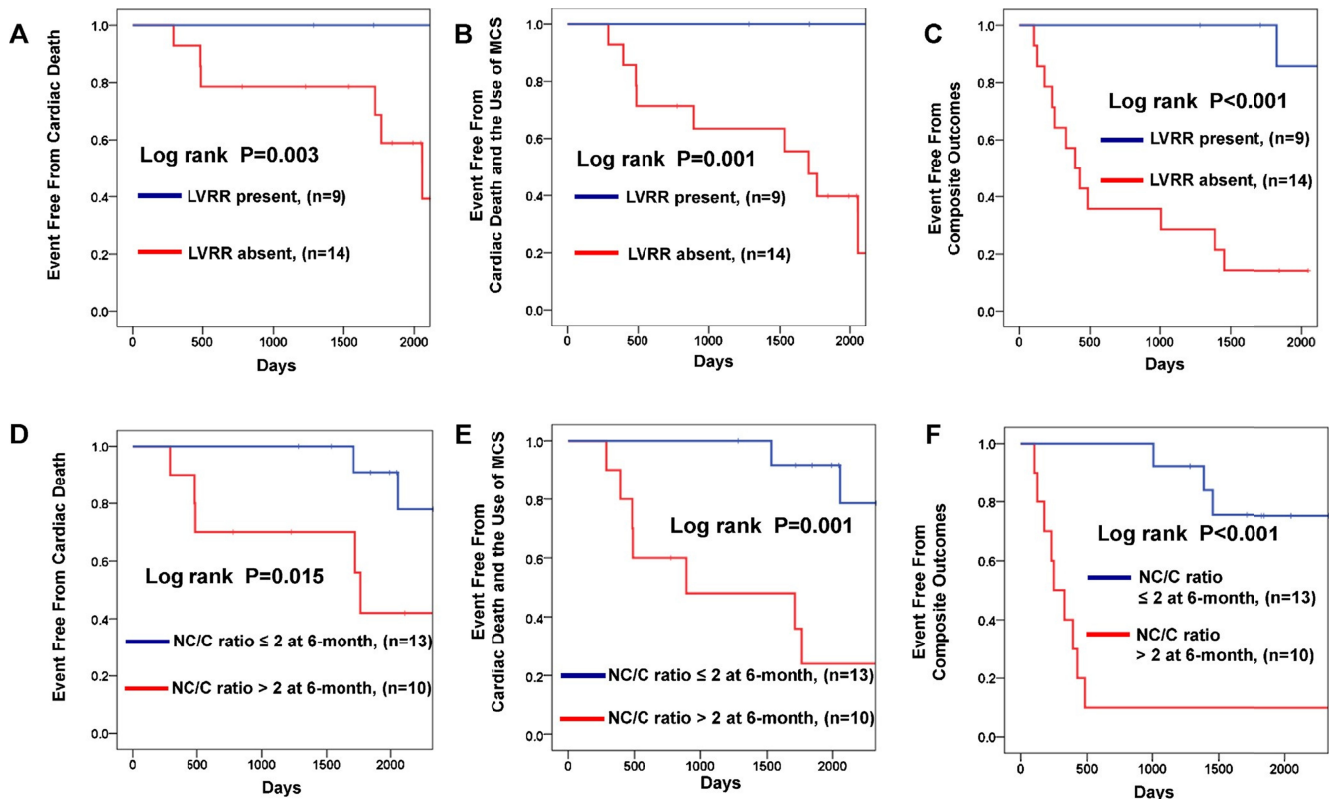


Fig. 4. Kaplan–Meier curves for (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the presence of LVRR. Kaplan–Meier curves for (D) cardiac death, (E) cardiac death and the use of MCS, and (F) composite outcomes according to the maximum ratio of the non-compacted to the compacted layer in the left ventricular myocardium. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVRR, left ventricular reverse remodeling; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

some patients with heart failure who have been subjected to an increased cardiac preload, as described in our study.

The major complications of LVNC are heart failure, arrhythmia, thromboembolic events, and sudden cardiac death [22,23]. However, little is known about the etiology, diagnostic criteria, incidence, or clinical outcomes associated with LVNC in adults [2]. In our study of adult patients with LVNC appearance, cardiac death occurred in 7 patients (30%) during a follow-up period of 61 months. Oechslin et al. reported the characteristics and outcomes in 34 adults with LVNC, among whom there were 12 deaths (35%) during a follow-up period of 44 months [5]. This was similar to our results.

Previous studies of patients with LV systolic dysfunction found that LVRR in those patients is associated with a favorable prognosis [24–27]. Merlo et al. reported that LVRR in idiopathic dilated cardiomyopathy patients was found in 89 of 242 patients (37%) and patients with LVRR showed a better prognosis compared to those without LVRR during 110 months [24]. However, there are no data regarding the relationship between LVRR and prognosis in patients with LVHT. In our study, patients with LVRR showed a better prognosis compared to those without LVRR, and this phenomenon is similar to those in patients with dilated cardiomyopathy. A recent report about the prognostic impact of LVHT in patients with dilated cardiomyopathy demonstrated that the cardiovascular events did not appear to be influenced by the degree of LVHT at baseline [28]. In our study, there was no difference in the degree of LVHT between the patients with LVRR and without at baseline. Therefore, it is difficult to elucidate the prognosis for cardiovascular events only in terms of the baseline LVHT degree. We firstly demonstrated that the regression of the LVHT, assessed by changes in NC/C ratio and LVHT area, during

the follow-up period had a clinical impact on cardiovascular events in patients with LVHT.

Jenni's echocardiographic criterion, namely a NC/C ratio of >2 obtained at end-systole in a parasternal short-axis view, is the most commonly used criterion for the detection of LVNC [10,29–31]. It has previously been validated against dilated cardiomyopathy, hypertensive heart disease, and valvular heart disease and showed good sensitivity and specificity [32,33]. For this reason, we used Jenni's echocardiographic criteria for the selection of the patients in our study.

Our findings demonstrated that some patients showed regression of LVHT, suggesting that LVHT could be reversible. However, it is difficult to reconcile this with the view of LVNC as a primary and genetic cardiomyopathy. Kohli et al. reported that 30 patients (15%) fulfilled Jenni's echocardiographic criteria for LVNC out of 199 patients with LV systolic dysfunction in a single center [4]. This study demonstrated current echocardiographic diagnostic criteria are too sensitive and result in over-diagnosis of LVNC in patients with LV systolic dysfunction as shown in our study. Therefore, we should consider that we might sometimes misclassify a transient cardiomyopathy as LVNC with the use of current morphological criteria alone [7].

#### Clinical implications

Our study demonstrated that patients without LVRR had a worse prognosis. Patients without LVRR were older and the use of cardiac resynchronization therapy and aldosterone antagonists at 6 months' follow-up was significantly more common than in patients with LVRR. Differences in the patients' characteristics might have been influenced by diagnoses in different phases of the

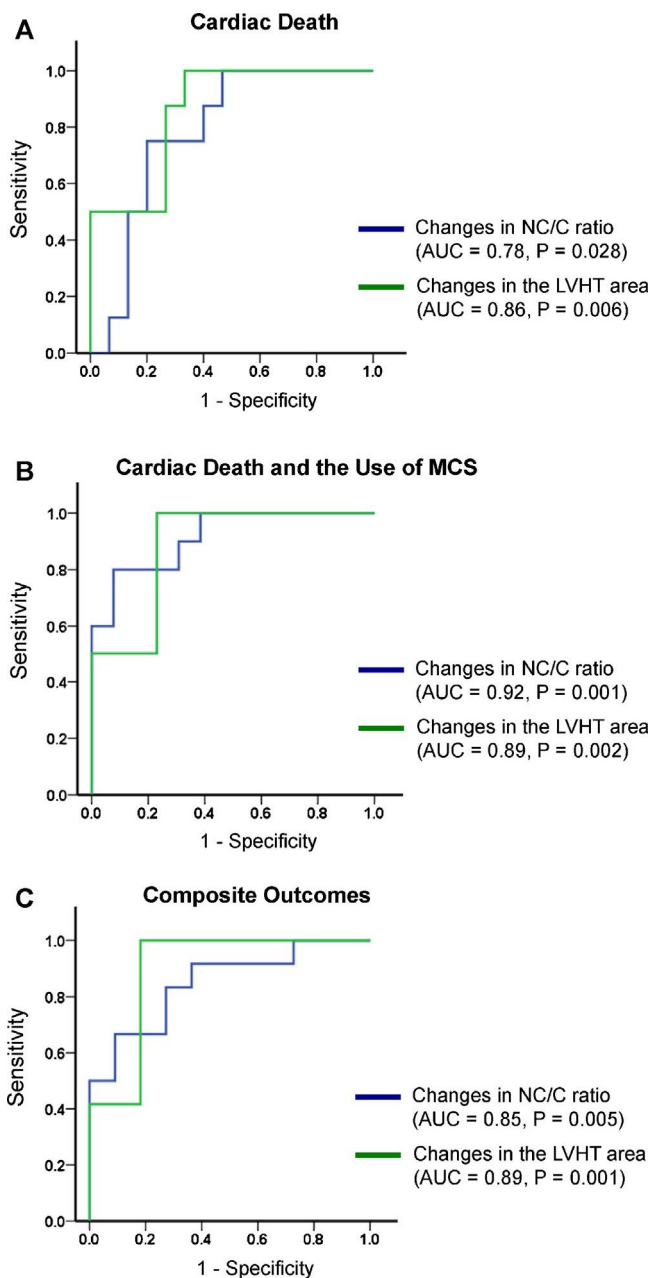


Fig. 5. Receiver-operating characteristic (ROC) curves for predicting (A) cardiac death, (B) cardiac death and the use of MCS, and (C) composite outcomes according to the changes in the maximum ratio of the NC/C in the left ventricular myocardium and the changes in LVHT area from baseline to 6 months' follow-up. Composite outcomes were cardiac death, the use of mechanical circulatory support, and hospitalization of heart failure. LVHT area, left ventricular hypertrabeculation area; MCS, mechanical circulatory support; NC/C, the non-compacted to the compacted layer.

disease (lead-time bias) and have influenced the clinical course in our study. Therefore, the high adverse outcome rate in patients without LVRR necessitates early recognition and appropriate therapeutic intervention, such as the optimal timing of cardiac transplantation referral in patients without LVRR.

#### Study limitations

The major limitation of our study was being an observational single center study with a small number of subjects; thus our results should be interpreted cautiously until verified in large-scale multicenter studies. We could not perform propensity

matched survival analysis and multivariate regression analysis adjusting for confounding factors, including age, and treatment agents because the small number of patients in each group would not be favorable for the above statistical approach. Therefore, it is hard to justify that improved functional and clinical outcomes are related to LVRR in our study. Second, no other cardiac imaging modalities for the quantification of LVHT or myocardial fibrosis, such as cardiac magnetic resonance imaging, were used. We could not perform cardiac magnetic resonance imaging because some patients with LVHT already had cardiac resynchronization therapy devices implanted. Third, our study did not allow speculation about the pathophysiology of the regression of LVHT and the prediction of LVRR. Indeed, we did not analyze the changes in LV mass and regional LV systolic function using 2D echocardiography. It was difficult to elucidate the changes in LV mass because there was no appropriate measurement of LV myocardium mostly in the non-compacted layer. Fourth, endomyocardial biopsy from the right ventricle was performed in 20 patients mostly one time. We might be unable to exclude completely inflammatory cardiac diseases during the follow-up period. Despite these limitations, our findings provide new insight into the relationship between the regression of LVHT, improvement in cardiac systolic function, and prognosis in patients with LVHT, which may be compatible with the diagnosis of LVNC. It remains unclear whether the presence of LVHT is sufficient to explain the influence of clinical outcomes in adult patients with LVHT compared to those in patients without LVHT. Further large-scale multicenter studies are needed to confirm the prognostic significance of regression of LVHT in patients with LV systolic dysfunction and to also perform multivariate analysis to identify factors that predict patient prognosis.

#### Conclusions

Regression of LVHT is associated with improvement in LV systolic function, and might be associated with a favorable prognosis in patients with LVHT who fulfill the echocardiographic criteria for LVNC.

#### Conflicts of interest

No conflicts of interest in this study.

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