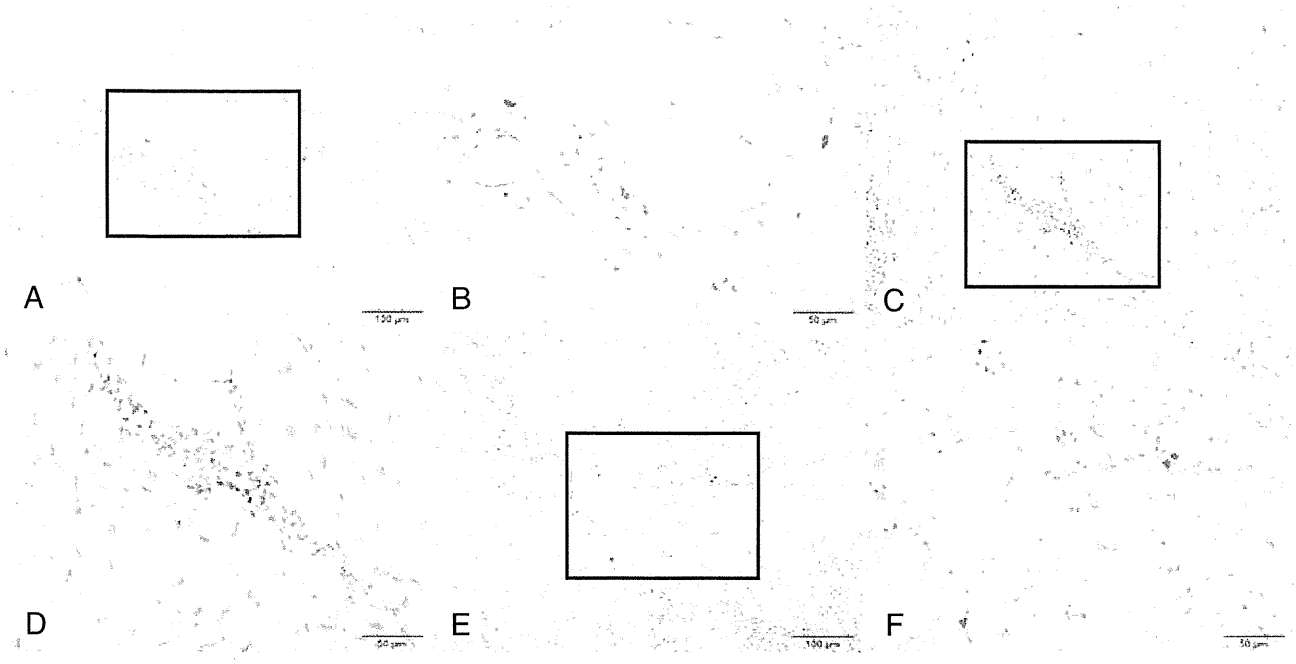

Fig. 5 IgG4 staining. Images of cardiac specimens that were judged to be "1+" on IgG4 staining are shown. A, Cardiac specimen from case 2. B, Higher-magnification image of the boxed area in A. C, Cardiac specimen from case 3. D, Higher-magnification image of the boxed area in C. E, Cardiac specimen from case 5. F, Higher-magnification image of the boxed area in E. (Original magnification: ×40 in A, C, and E and ×100 in B, D, and F.)

sclerosing disease has not been fully discussed so far. Our data suggest that sarcoidosis, which had been diagnosed as such at our institute, may not be a misdiagnosis of or overlap with IgG4-related sclerosing disease. Given that a population of greater than 50% IgG4-positive infiltrated plasma cells is a prerequisite condition for diagnosing IgG4-related sclerosing disease [5], this notion is supported, especially in cardiac sarcoidosis, by the findings from immunohistochemical analysis such as the absence or sparse presence of IgG4-positive cells in sarcoid granulomas in cardiac tissue and lymph nodes (Figs. 2 and 3), even in the presence of mildly elevated serum IgG4 levels. In addition, it has recently been reported that IgG4-related sclerosing disease may be characterized by predominant activation of the T-helper 2-mediated immune reaction [17]. In contrast, our previous finding indicated that cardiac sarcoidosis is characterized by activation of the T-helper 1-mediated immune response [18].

The strength of the current study is that we could perform immunohistochemical analysis on several cardiac tissues obtained from left ventriculoplasty, enabling the screening of numerous cardiac tissue samples from a variety of locations from patients presumably having extensive granulomatous degeneration of the heart. However, our study has several limitations. First, histologic assessment was not possible for all patients with cardiac sarcoidosis who were subjected to serum IgG4 measurement. Second, granuloma-positive noncardiac tissue was not stained for IgG4 in non–cardiac sarcoidosis patients; therefore, the prevalence of histologic IgG4 positivity is not available for these patients. Third, although none of the patients with cardiac sarcoidosis had a history of corticosteroid therapy at the time of blood sampling and/or tissue acquisition, a few non–cardiac sarcoidosis patients had already been taking steroid drugs at the time of blood sampling.

In conclusion, among the 65 patients diagnosed with sarcoidosis, the mean serum IgG4 level was 56.8 ± 43.0 mg/dL. The mean serum IgG4 level and the prevalence of an IgG4 level above the upper reference range did not significantly differ between patients with cardiac sarcoidosis and non–cardiac sarcoidosis patients. Immunohistochemical staining of cardiac and lymph node samples from patients with cardiac sarcoidosis showed only sparse or no infiltration of IgG4-positive lymphocytes, in contrast to the moderate to severe infiltration of CD68-positive macrophages and CD45-positive lymphocytes. In conclusion, it appears that among patients with sarcoidosis, especially among patients with cardiac sarcoidosis, the infiltration of IgG4-positive lymphocytes is, when present, only sparse, supporting the notion that sarcoidosis does not belong to or overlap with IgG4-related sclerosing disease.

Supplementary data

Supplementary materials related to this article can be found online at doi:10.1016/j.humpath.2011.07.002.

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References

[1] Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732-8.
[2] Ito H, Kaizaki Y, Noda Y, Fujii S, Yamamoto S. IgG4-related inflammatory abdominal aortic aneurysm associated with autoimmune pancreatitis. Pathol Int 2008;58:421-6.
[3] Van Moerkercke W, Verhamme M, Doubel P, Meeus G, Oyen R, Van Steenbergen W. Autoimmune pancreatitis and extrapancreatic manifestations of IgG4-related sclerosing disease. Acta Gastroenterol Belg 2010;73:239-46.
[4] Bateman AC, Deheragoda MG. IgG4-related systemic sclerosing disease—an emerging and under-diagnosed condition. Histopathology 2009;55:373-83.
[5] Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis 2009;68:1310-5.
[6] Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4–related lung disease: CT findings with pathologic correlations. Radiology 2009;251:260-70.
[7] Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. Am J Gastroenterol 2003;98:2811-2.
[8] Takeda N, Hirata Y, Nagai R. Cardiovascular complications of retroperitoneal fibrosis. Kokyu to Junkan 2007;55:441-7 (in Japanese).
[9] Sugimoto T, Morita Y, Isshiki K, et al. Constrictive pericarditis as an emerging manifestation of hyper-IgG4 disease. Int J Cardiol 2008;130: e100-1.
[10] Iwai K, Sekiguti M, Hosoda Y, et al. Racial difference in cardiac sarcoidosis incidence observed at autopsy. Sarcoidosis 1994;11:26-31.
[11] Rybicki BA, Major M, Popovich Jr J, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 1997;145:234-41.
[12] Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 1978;58:1204-11.
[13] JCS Joint Working Group. Guidelines for diagnosis and treatment of myocarditis (JCS 2009): digest version. Circ J 2011;75:734-43.
[14] Kasahara Y, Ashihara Y. Colorimetry of angiotensin-I converting enzyme activity in serum. Clin Chem 1981;27:1922-5.
[15] Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest 2003;124:186-95.
[16] Masaki Y, Umehara H. IgG4-related disease-the diagnostic confusion and how to avoid it. Nihon Rinsho Meneki Gakkai Kaishi 2009;32: 478-83.
[17] Zen Y, Nakanuma Y. Pathogenesis of IgG4-related disease. Curr Opin Rheumatol 2011;23:114-8.
[18] Terasaki F, Ukimura A, Tsukada B, et al. Enhanced expression of type 1 helper T-cell cytokines in the myocardium of active cardiac sarcoidosis. Circ J 2008;72:1303-7.

連載
CPC解説

拡張型心筋症として診断，治療されていた一剖検例

▶▶▶第55回

松山高明*，植田初江*

はじめに

拡張型心筋症 dilated cardiomyopathy (DCM) は心房・心室腔の拡大と心室壁の全周性の菲薄化を示す心筋症の形態学的総称で，主に原因が不明なものを示す病名であり，その中には様々な病因によるものが含まれている．病理解剖でもDCMを経験する機会は稀ではないが，臨床の現場では患者の状態や各医療施設の設備状況により十分な検討がなされないままに原因が不明という理由でDCMの診断がなされて治療されていることもある．病理解剖では最終的にDCMと類似の形態を呈する原因が明らかな二次性心筋症や他の特発性心筋症を除外して最終的に診断を確定する必要がある．

Ⅰ．臨床的事項

1．症　例

【年齢・性別】 70歳代，男性．

【既往歴】 気管支喘息(50歳～)，十二指腸潰瘍(62歳，胃2/3切除後)．

【嗜好歴】 喫煙：20本/20年(40歳まで)，飲酒：日本酒1升/日(68歳まで)．

【家族歴】 姉：突然死(30歳代)，娘：DCMの疑い．

【現病歴】 10年前より呼吸困難感が出現．NYHA Ⅱ度の心不全と診断された．他院で心臓カテーテル検査(冠動脈造影では冠動脈狭窄像なし)や心臓超音波検査などの所見から臨床的にDCMと診断され，利尿薬やβブロッカーの投与を開始された．8年前には失神を認め救急搬送．心室頻拍/細動(VT/VF)を認めたためアミオダロンの投与を開始し，植え込み型除細動器 implantable cardioverter defibrillator (ICD) の適応となった．その後も心不全による労作時の呼吸苦は持続し，血液検査ではBNP (brain natriuretic peptide) は約1,000～2,000 pg/mLの高値を示すことも多く，7年前からは心臓再同期療法(両室ペーシング機能付き植え込み型除細動器：CRT-D)を開始．やや心不全症状は軽快し，VTの出現頻度も減少したものの，その後も慢性的に心不全の状態は続き，外来受診時にX線上胸水の貯留を認め，BNPが6,574.1 pg/mLまで上昇したため，心不全の増悪と診断され入院した．

2．入院時所見

【身体所見】 身長161 cm，体重41 kg，血圧77/54 mmHg，心拍数70回/分，呼吸回数18回/分，体温36.7℃，動脈血酸素飽和度96％(room air)，眼瞼結膜は貧血様，眼球結膜は黄染なし，頸静脈の怒張あり，頸部リンパ節腫大なし，甲状腺腫大なし，心音は整，S1→S2，S3(－)，S4(－)，収縮期雑音はLevine Ⅲ/Ⅳ，呼吸音は両下肺野の呼吸音低下，ラ音なし，腹部は平坦，軟，腸管蠕動音異常なし，下腿浮腫軽度認める．

【血液検査】 WBC 6,400/μL，RBC 236万/μL，Hb 8.0 g/dL，Ht 23.7％，MCHC 33.7％，PLT 19.7万/μL，T-P 5.9 g/dL，Albumin 3.4 g/dL，T-Bil 0.4 mg/dL，ASL 20 IU/L，ALT 12 IU/L，LDH 171 IU/L，CK 42 IU/L，Na 133 mEq/L，K 4.5 mEq/L，Cl 94 mEq/L，Ca 8.6 mg/dL，BUN 100 mg/dL，Cr 5.3 mg/dL，UA 12.4 mg/dL，BS 95 mg/dL，CRP 0.6 mg/dL，PT-INR 1.72，BNP 6,574.1 pg/mL．

【胸部単純X線】 心陰影の拡大，左横隔膜角の鈍化および肺血管陰影の増強を認める(**図1a**)．

【12誘導心電図】 心拍数70回/分，CRT-Dによる心房，心室ペーシング(**図1b**)．

【心臓超音波検査(**図2**)】 左室拡張末期径(LVDD) 74 mm，左室収縮末期径(LVDS) 66 mm，左室内径短縮率(％FS) 11％，左室駆出率(EF (Simpson法)) 16％，僧帽弁逆流(MR) 2/4，大動脈弁逆流(AR) 2/4，三尖弁圧較差(TRPG) 35 mmHg，左室壁は全周性に菲薄化していたが，特に中隔の菲薄化が著明であった．

【右心カテーテル】 PA 44/19 (mean 28) mmHg，RV

*国立循環器病研究センター臨床検査部 臨床病理科

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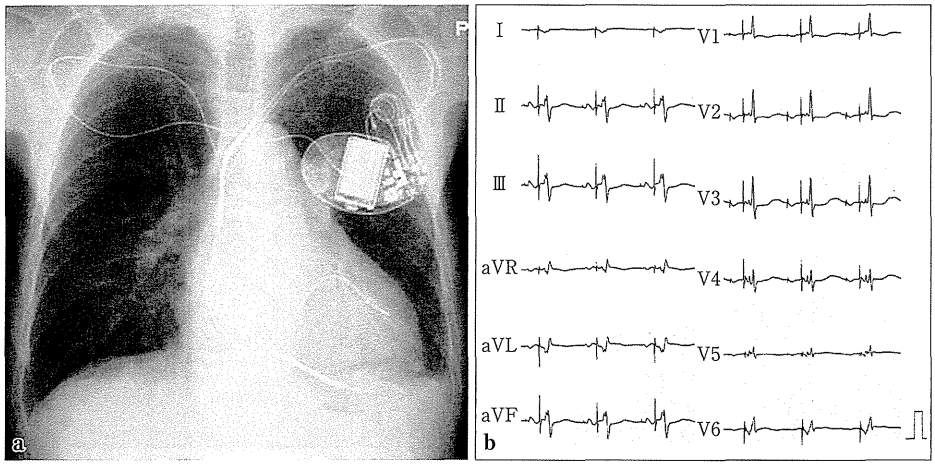


図1　入院時の胸部X線および心電図所見
a：胸部X線．両室ペーシング機能付きの埋め込み型除細動器が留置されている．
b：12誘導心電図．心拍数70回/分，心房，心室ペーシングリズム．

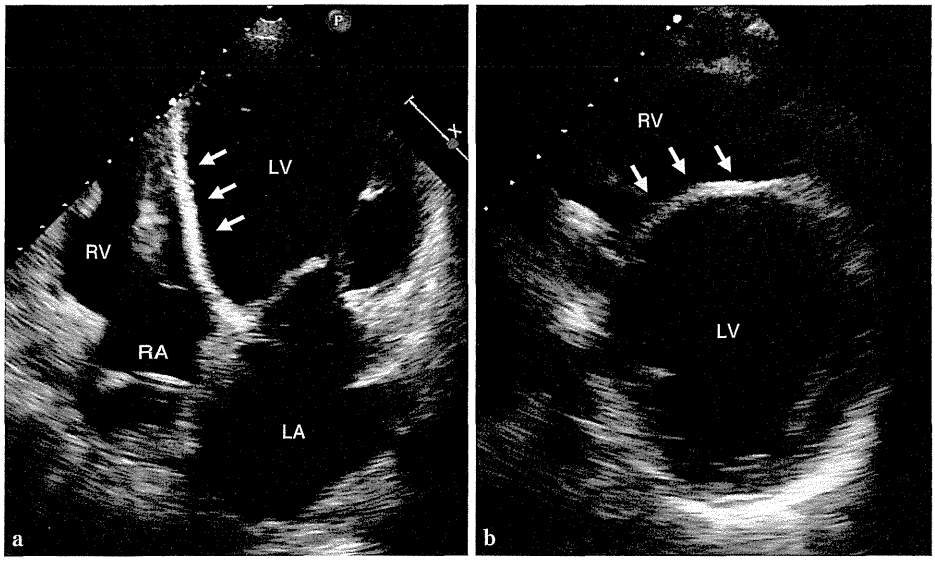


図2　心臓超音波所見
a：四腔断面像，b：両心室短軸断面像．
矢印は菲薄化した中隔を示す．
LA：左房，LV：左室，RA：右房，RV：右室．

42/8 mmHg，PCW（肺動脈楔入圧）20 mmHg，CO 2.6/min，CI 1.9 L/min/m^2．

3．入院後経過

低心拍出症候群 low output syndrome（LOS）の状態で，カテコラミンの投与等の心不全治療を開始した．入院後からはVTが出現し，ICDが頻回に作動するためアミオダロンの静注を開始．一時的に軽快したものの再度VTが出現し，その後もうっ血による低Na血症の進行，肝酵素の上昇などがみられ，心不全も治療に対して効果なく，入院後2ヵ月の経過で死亡した．

Ⅱ．病理への検索希望事項

1．拡張型心筋症の形態および病因
2．心不全の腎臓への影響

Ⅲ．病理解剖所見

死後18時間で頭部を除く全身解剖を行った．

・全身所見：身長161 cm，体重41.4 kgの高齢男性．左鎖骨下の皮下にペースメーカのジェネレータが留置され，正中季肋部から臍上まで手術瘢痕を認めた．腹水は黄色透明で900 mL貯留していた．
・心臓：心重量は685 gと著明な重量増加を認め，心尖部は左室から形成され，鈍角化していた（**図3**）．灌流固定後の四腔断面では，四心腔ともに拡大しており，左室では全周性に壁の菲薄化がみられ，特に心室中隔は貫壁性の線維化を伴って著しく菲薄化していた．ペースメーカリードが右心耳，右室心尖部，冠静脈洞内（左室ペーシング用）に留置されていた（**図4**）．肉眼的には心内膜面に血栓の付着や，弁尖への疣贅の付着はなかった．両心

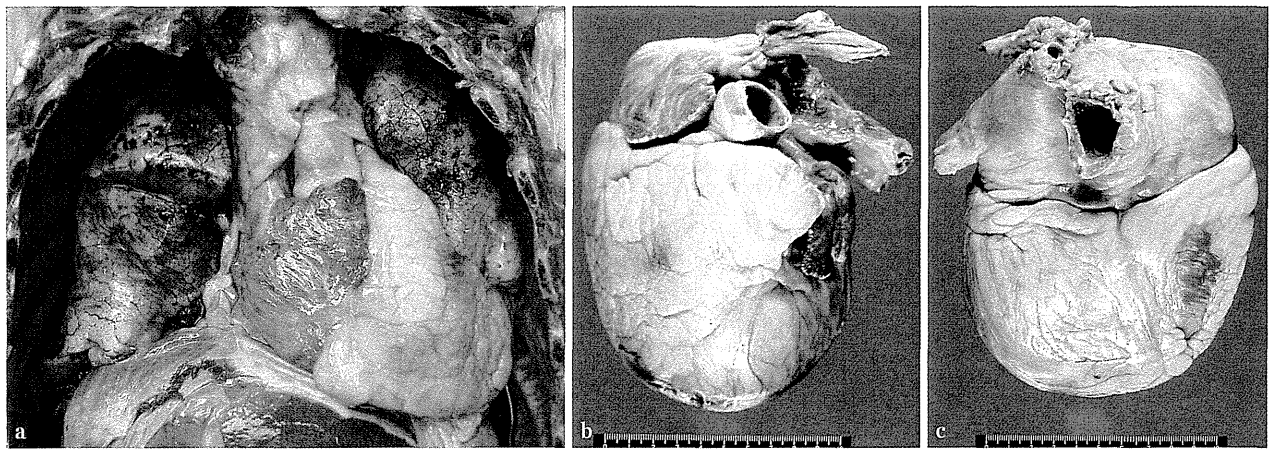
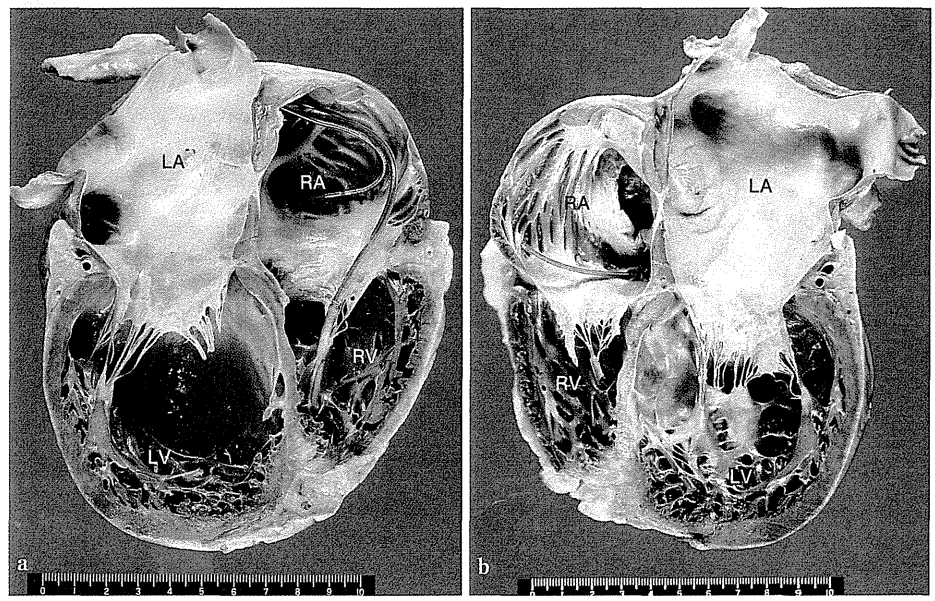


図3　剖検時の心臓　a：剖検時胸郭内の心臓，b：心臓前面，c：心臓後面．心尖部は鈍角化して心臓は円形を呈している．

図4　四腔断面肉眼像
a：前壁方向を見た図，b：後壁方向を見た図．
四腔ともに著明に拡大し，心室では特に中隔の線維菲薄化が目立つ．ペースメーカリードが留置されている．
LA：左房，LV：左室，RA：右房，RV：右室．



室短軸断面では全周性に左室壁が菲薄化し，特に中隔から前後両室接合部にかけて広範囲に区域性の線維化を認めた（**図5**）．組織学的には心外膜および中層から広がる帯状の置換性線維化が主体で中隔全体に広がっていた．線維化部周辺の心筋細胞は配列が乱れ，錯綜配列を示していた．個々の細胞も大小不同が著しく，分岐の異常と核の変形・腫大が著明であった．中隔の線維置換部分では小動脈は壁が著明に肥厚し内腔が狭窄していた（**図6**）．心外膜の冠動脈は軽度の動脈硬化像を示すのみで内腔の有意な狭窄はみられなかった．刺激伝導系では洞結節は年齢相応の萎縮を示し，房室結節からHis束-左脚も線維化および萎縮がみられたが，中隔の線維化病変の直接的な波及はみられなかった（**図7**）．また，全体的に心筋炎やサルコイドーシスなどの炎症性疾患を示唆する炎症細胞浸潤はみられなかった．以上の特徴から拡張相肥大型心筋症 hypertrophic cardiomyopathy，dilated phase（d-HCM）が最も考えられた．

- 肺：重量は左が520 g，右が765 gであった．右肺の表面には気腫性のブラの形成を認め，割面でも小型の嚢胞状変化がびまん性にみられ，肺気腫の像であった．組織学的にも肺胞構造は壊れ，不規則な気腔の拡大と気管支の拡大がみられた．また，うっ血水腫の像もみられた．肺門部のリンパ節では炭粉沈着を認めるのみで，肉芽腫の形成などはみられなかった（**図8**）．
- 肝胆：肝臓の重量は630 g．胆嚢は腫大し，胆汁排泄はやや不良であった．自己融解がみられ，肉眼的に萎縮しているが，肉ずく様を呈しており，組織学的にも中心静脈の拡大がみられ，うっ血肝の像であった．

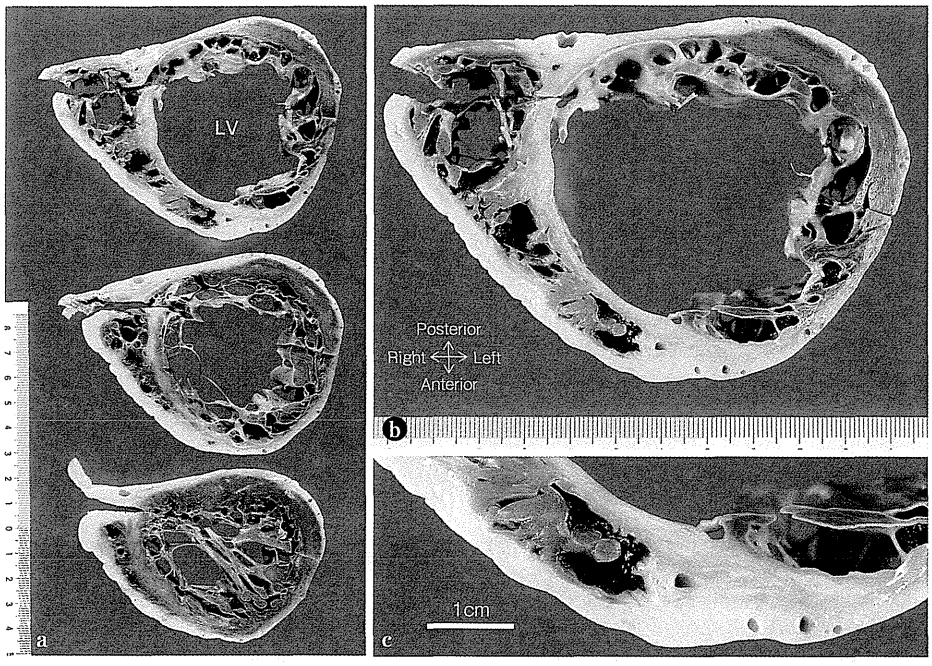


図5　両心室短軸断面像　全周性に左室壁は菲薄化しており，乳頭筋レベルより心基部側で貫壁性の高度の線維化がみられる．

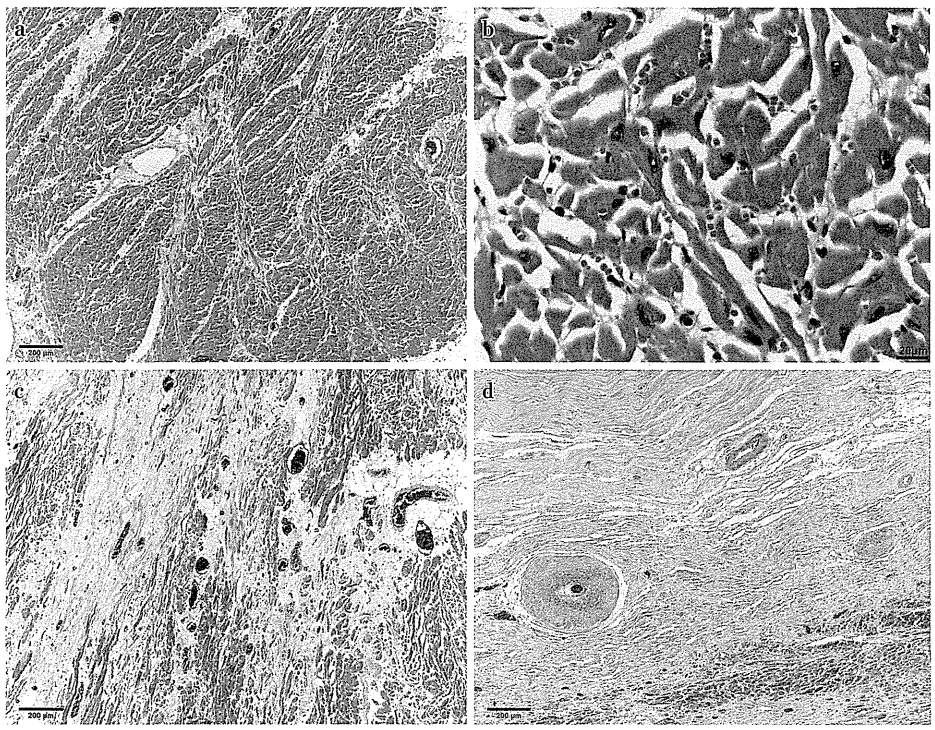


図6　心臓の組織像
a：線維化部分周辺の心筋では錯綜配列が目立つ．
b：心筋細胞は大小不同が著明で，核の腫大や変形がみられる．
c：Masson trichrome染色．線維化は置換性の線維化が主体である．
d：Masson trichrome染色．線維化部分の小動脈は壁が肥厚して内腔の狭窄したものが目立つ．

・腎臓：重量は左が60 g，右が60 gで萎縮し，表面は細顆粒状を呈し，左側には嚢胞がみられ，皮質の菲薄化がみられた．組織学的には糸球体の全硬化が目立ち，小動脈壁も硝子化とともに狭窄したものが目立ち，良性腎硬化症の像であった（図9）．

Ⅳ．病理学的診断

【主病変】

①拡張相肥大型心筋症（d-HCM）［臨床診断：拡張型心筋症］（心重量685 g）

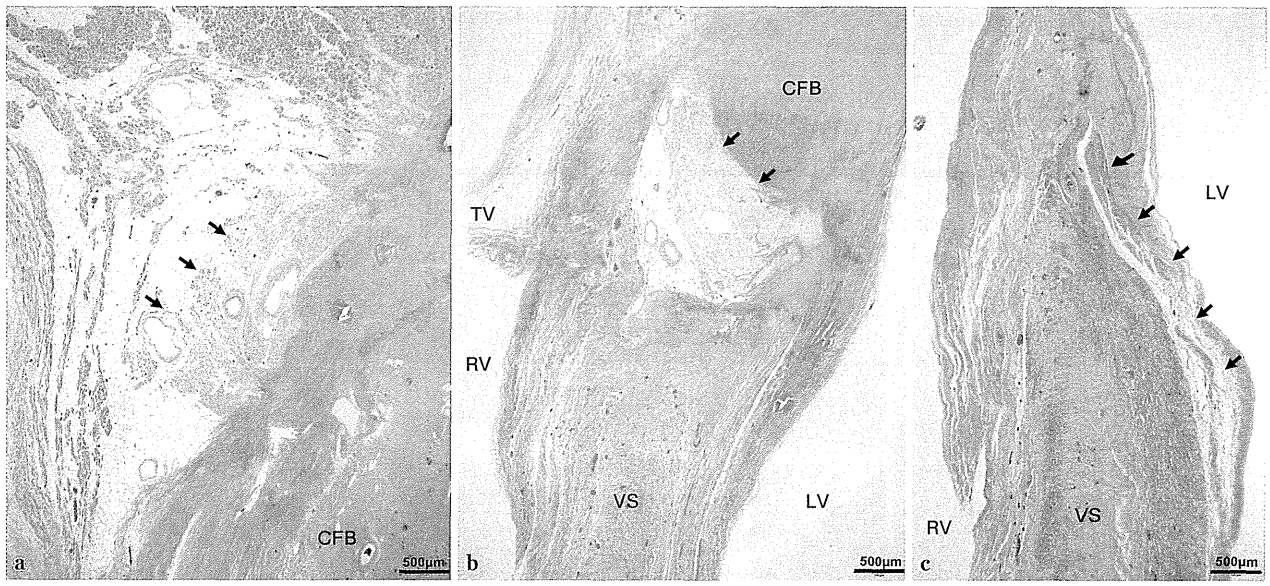


図7　刺激伝導系の組織像（Masson *trichrome* 染色）　a：房室結節（矢印），b：His 束（矢印）は周囲に脂肪化がみられやや萎縮傾向にあるが，脱落はみられない．c：His 束-左脚分岐部（矢印）周囲に線維化が隣接し，左脚の線維化もみられるが完全には脱落していない．CFB：中心線維体，LV：左室，RV：右室，TV：三尖弁，VS：心室中隔．

・貫壁性左室壁線維菲薄化（前壁から中隔全域にかけて）
・心室壁厚
　左室：前壁4 mm，側壁5 mm，後壁8 mm，中隔4 mm
・線維化部分の周囲に心筋錯綜配列が目立つ，線維化巣周囲の小動脈の壁の肥厚と内腔狭窄
・心外膜の冠動脈の有意狭窄なし
　洞結節：萎縮，房室結節-His 束：軽度萎縮
②［心室頻拍］難治性心室性不整脈および心不全に対する心室再同期療法後（CRT-D 留置後）
・上大静脈内リード癒着および血栓閉塞

【副病変】

①腔水症（胸水貯留，腹水貯留900 mL，淡黄色透明）［心不全による］
②うっ血肝（630 g），胆嚢腫大
③肺気腫（小葉中心性）および肺うっ血，右肺ブラ形成（左520 g，右765 g）
・肺門リンパ節には肉芽腫性病変なし
④良性腎硬化症，陳旧性腎梗塞，腎萎縮，尿細管萎縮および壊死（左60 g，右60 g）
⑤大動脈粥状硬化症（腸骨動脈分岐部血栓）
⑥胃幽門部切除後［十二指腸潰瘍による］
・幽門側断端部13×10 mm の過形成性ポリープ，良性

V．病理からの返答

1．拡張型心筋症の形態および病因

サルコイドーシスと d-HCM の鑑別が重要となる肉眼像であるが，心臓以外の他臓器にサルコイドーシスを示唆する肉芽腫や線維瘢痕がなく，組織像では心筋の錯綜配列が顕著に目立つ部分が線維化周囲にみられ，心筋症の家族歴があることを考慮すると d-HCM の終末像をみていると考えられる．

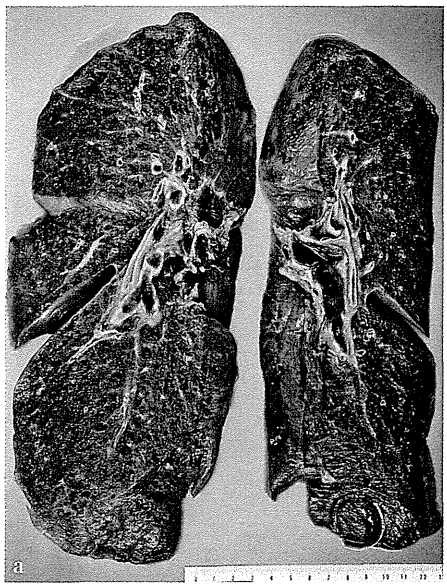
2．心不全の諸臓器（肝臓・腎臓）への影響

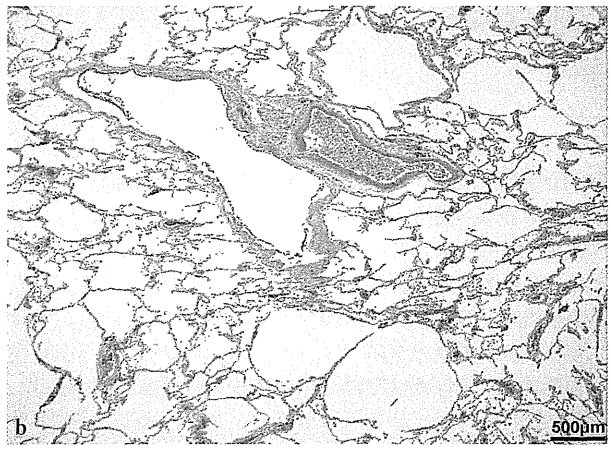
肝臓は中心静脈周囲の高度のうっ血像がみられる．腎臓は心不全に関連した腎不全による尿細管萎縮および壊死像がみられた．高齢でもあり，動脈硬化性の変化も加わっている．

Ⅵ．考察と鑑別診断

心不全により死亡した症例の病理解剖は多く経験する．その中には心臓が拡大し臨床診断を DCM として診断・治療をされていた症例もあり，時にその臨床診断が妥当でないこともある．これは心臓疾患の病理学的な評価の機会がカテーテルによる心内膜心筋生検や開心術時の生検などに限られており，いずれも微少な検体しか得られず，特にカテーテルによる生検は病変部を選択的に採られたものではなく，どうしてもサンプリングエラーが多くなるためである．そのため，ほかに超音波検査，CT，MRI，核医学検査やカテーテル検査など一連の画像検査を総合してもなお，心腔の拡大のみで特異的な所見が得られなければ，差し当たって DCM の診断がなされてしまうこともある．病理解剖ではこのような症例の心臓全体を詳細に評価できるため，その解析結果は臨床医へのフィードバックのためにも非常に重要である．

DCM と同様の形態を呈し，DCM との鑑別が重要な疾





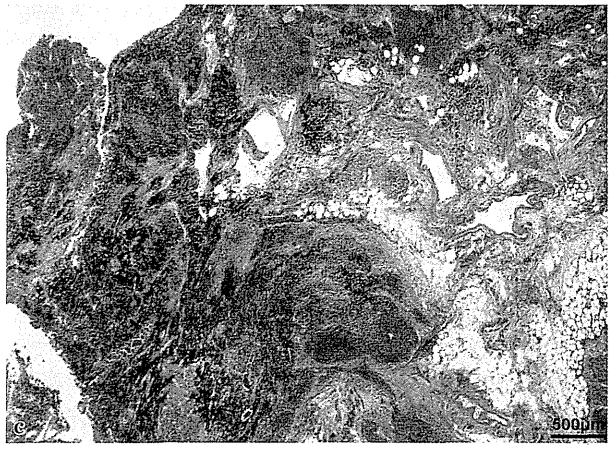
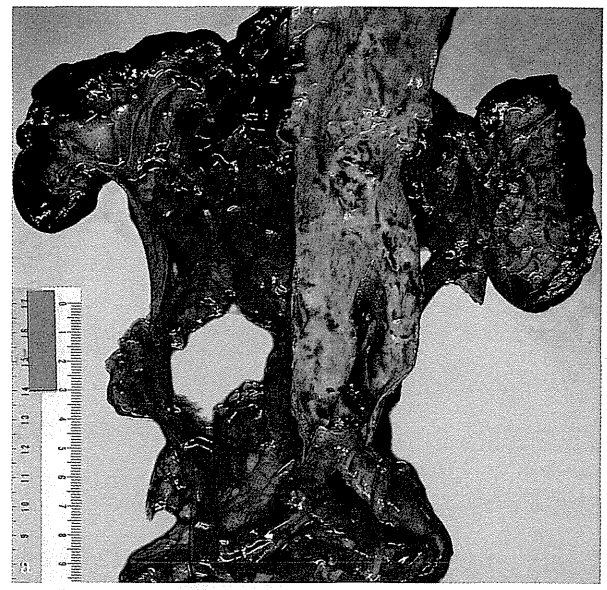
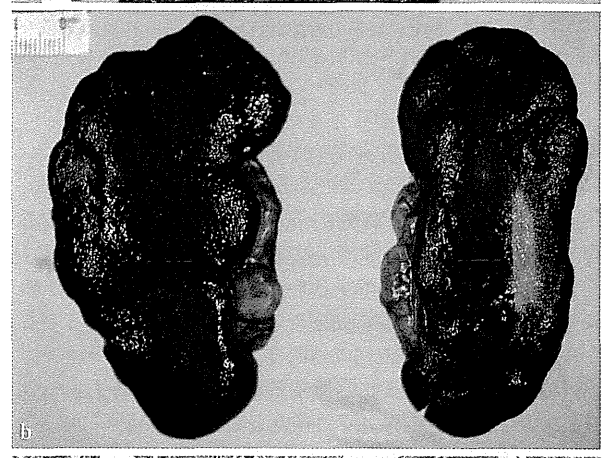


図8　肺　a：肺割面肉眼像．全体的に大小嚢胞を形成し肺気腫の像である．b：肺胞構造が破壊され嚢胞様を呈している．気管支も拡張している．c：肺門部リンパ節は腫大していたが，組織学的には肉芽腫の形成や線維瘢痕はみられなかった．





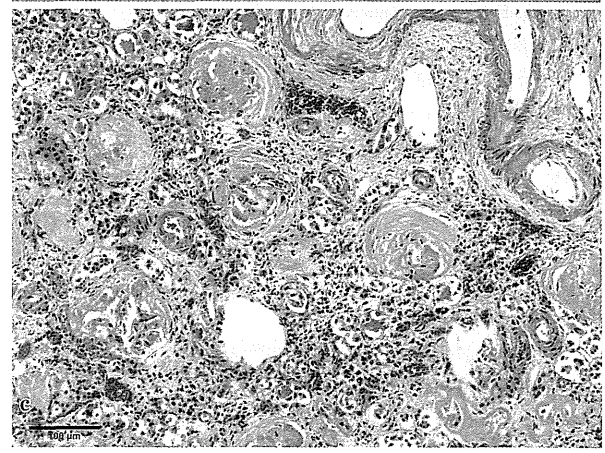
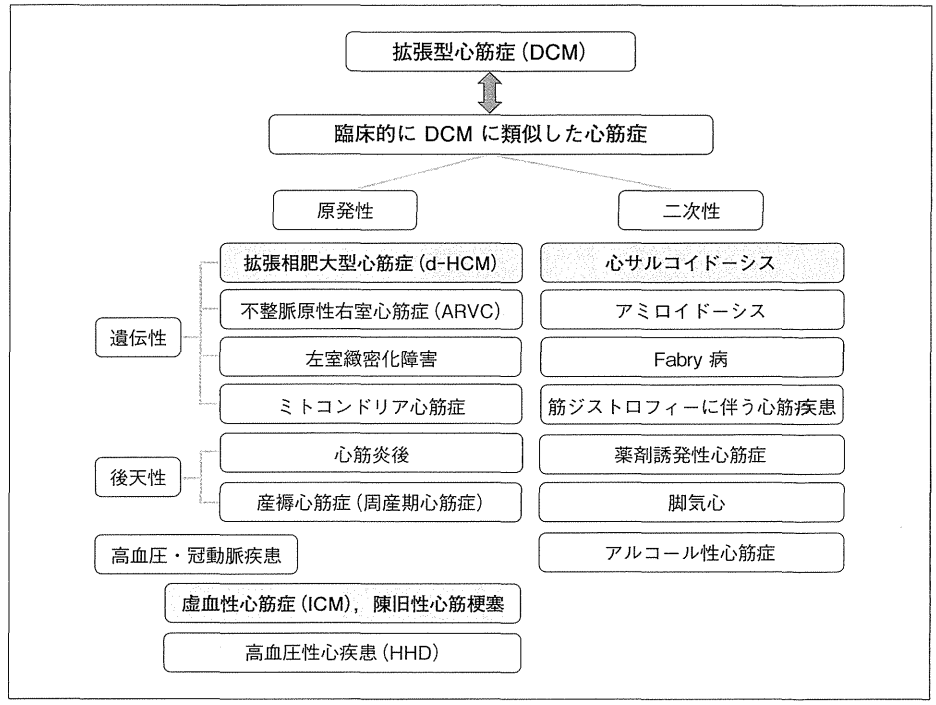


図9　腎臓と腹部大動脈　a：腎臓は両側ともに萎縮がみられる．b：腎表面は細顆粒状で，左下極には嚢胞がみられる．c：糸球体は全硬化に陥ったものが多く，小動脈の硝子化による硬化像や非特異的なリンパ球の浸潤がみられる．

図10　拡張型心筋症とそれに類似する心筋症（文献1より改変）



患を**図10**に示した[1]．DCMは組織学的には心筋細胞間にびまん性に広がる間質線維化が典型的であり，区域性に心筋が脱落して置換性に線維に置き換わり，部分的に著明な壁菲薄化を呈することは少ない[2]．しかし，本例は病理解剖で特異な広範囲の置換性線維化をきたしていた．このような置換性の線維化をみた場合は**図10**の緑色で示した，①虚血性心筋症（陳旧性心筋梗塞），②心サルコイドーシスと③d-HCMの鑑別が特に重要となる．

①虚血性心筋症（陳旧性心筋梗塞）

虚血性心筋症ischemic cardiomyopathyはBurchら[3]により提唱された名称で，高度の冠動脈狭窄病変（閉塞している必要はない）を有し，広範囲に虚血による線維化が広がり心腔が拡張した病変を示す総称であり，現在は臨床医の間で高度の冠動脈病変とともにびまん性の心室壁運動の低下をきたしている状態に用いられ，病理学的には冠動脈を検索して，閉塞病変とそれに一致する区域性の大きな線維化病変を認めた場合は，心腔が拡張していたとしても陳旧性心筋梗塞と記載するのが望ましい．心内膜を主体にする線維化の範囲と，冠動脈の狭窄所見と併せて評価する．**図11a**の両心室横断面はBurchらの提唱した古典的な虚血性心筋症といえる一例で，左冠動脈に90％以上の狭窄，右冠動脈に75％以上の狭窄を認めたものの，それぞれの冠動脈の支配領域に一致する区域性の大きな線維化病変は認めず，心内膜下に全周性の虚血性線維化が広がっている．一方，**図11b**は生前に冠動脈造影が行えず，DCMと診断されていた症例で，左室腔は拡大しているが，右冠動脈に完全閉塞があり，その支配領域に一致して後壁に貫壁性の区域性線維化があるため，病理学的診断は陳旧性心筋梗塞とするのが適当であった．

今回の症例は冠動脈病変がなく，線維化領域は冠動脈支配に一致せず，心外膜側を主体に広がっていることから虚血性心筋症とはパターンが異なっていた．

②心サルコイドーシス

サルコイドーシスは原因不明の肉芽腫性病変による疾患で，心サルコイドーシスは房室ブロック，心室性不整脈などの致死性不整脈による突然死や炎症の繰り返しによる広範囲の線維瘢痕による心不全が問題となる．サルコイドーシスは巨細胞を含む肉芽腫性病変を認めれば診断は容易であるが，先述のとおりカテーテルによる心筋生検では病変部を選択的に採取できないため，心サルコイドーシスの疑いのある症例で実際に生検により確定診断に至る割合は我々の経験では30％にも満たない．また，炎症をとらえる核医学検査のFDG-PET/CTや線維化をとらえるMRIの遅延造影などの画像検査も進歩してきてはいるが[4]，依然としてサルコイドーシスの診断が正しくなされないままDCMとして扱われている症例も多く存在する．サルコイドーシスの心室病変は多様性に富むが，**図11c**に示すように線維化病変は後部両室接合部から中隔方向に置換性に広がる傾向があり，心室中隔頂上部に達すれば房室ブロックや脚ブロックなどの伝導障害を生じるものと考えられる．このパターンは今回の症例の線維化のパターンと類似しているが，本例では他臓器を含め明らかな肉芽腫性病変は認めずサルコイドーシスは否定的であった．また，サルコイドーシスは炎症の再燃と消退を繰り返し緩徐に進行するた

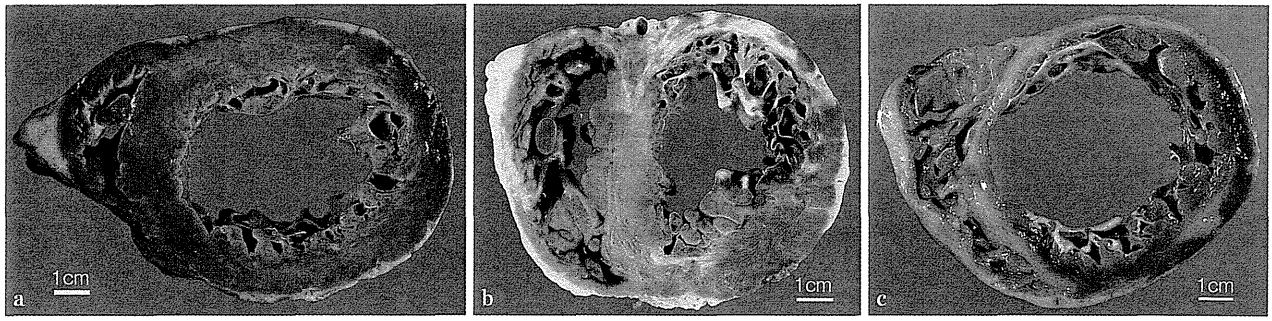


図11　本例と鑑別を要する疾患　a：冠動脈に完全閉塞病変を有さない虚血性心筋症の両心室横断面．b：冠動脈造影ができず，拡張型心筋症と診断されていた症例．右冠動脈に完全閉塞があり，その支配領域に一致して左室後壁に区域性の貫壁性の線維化がみられ，陳旧性心筋梗塞と診断した．c：サルコイドーシスによる心不全症例．中隔には高度の線維化病変がみられ，菲薄化している．

め，炎症の消退期や自然寛解した症例では組織学的に線維化のみを認め，活動性を示す肉芽腫病変を幾ら検索しても見出せないこともあるので，肺門部リンパ節や他の臓器の所見，臨床経過などとの照らし合わせも重要である．

③拡張相肥大型心筋症（d-HCM）

d-HCMの線維化の分布もサルコイドーシスと同様に多様性に富むが，終末像では本例のような貫壁性で区域性の著しい線維化をきたすことも多い．この線維化は冠動脈の支配域と一致せず，心外膜側を主体に広がることから，虚血性変化とは鑑別される．この疾患も重度の心不全に至るため，当センターではDCMに次いで2番目に多く心臓移植の対象になっている[5]．この広範な置換性線維化の成因は明らかにされていないが，線維化病変中の心筋間小動脈は壁が著しく肥厚し，内腔が狭窄したものが目立つためこの小動脈レベルの虚血が関与しているとする考え方があり，この病変はsmall intramural coronary artery dysplasia（SICAD）と称されている[6]．本例でも**図6d**に示すようにこの所見がみられた．中隔壁の菲薄化は著しく，一見肥厚した部分がなくHCMを想像するのは困難な肉眼像ではあったが，組織学的には線維化部分周辺で錯綜配列が顕著であり，d-HCMの診断に至った．また，詳細は不明であるが，突然死の家族歴は特発性心筋症であるHCMであった可能性を支持する情報である．

おわりに

waste basket様の病名であるDCMは，今後も遺伝子解析などのmolecular pathologyも駆使して病因を解明して治療につなげていく必要がある．病理解剖はその病態を明らかにするための基本的な手法として依然として重要である．また，近年は本邦でも心臓移植の件数が増加し，レシピエント心が外科病理検体として検索される機会も増え，その詳細な解析により中性脂肪蓄積心筋血管症など全く異なる疾患概念の疾患も見出されており，伝統的な病理形態学的検索はこれからも重要である[7]．

文　献

1) 拡張型心筋症ならびに関連する二次性心筋症の診療に関するガイドライン．循環器病の診断と治療に関するガイドライン．2009-2010年度合同研究班報告
2) Roberts, W.C., Siegel, R.J., McManus, B.M.：Idiopathic dilated cardiomyopathy：analysis of 152 necropsy patients. Am J Cardiol 1987, **60**：1340-1355
3) Burch, G.E., Tsui, C.Y., Harb, J.M. et al.：Ischemic cardiomyopathy. Am Heart J 1972, **83**：340-350
4) Ohira, H., Tsujino, I., Ishimaru, S. et al.：Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nucl Imaging 2008, **35**：933-941
5) 植田初江，池田善彦，松山高明 他：心臓移植の病理—50例の経験—．日病会誌 2012，**101**：27
6) Kwon, D.H., Smedira, N.G., Rodriquez, E.R. et al.：Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy：correlation with histopathology and prevalence of ventricular tachycardia. J Am Coll Cardiol 2009, **54**：242-249
7) Hirano, K., Ikeda, Y., Zaima, N. et al.：Triglyceride deposit cardiomyovasculopathy. N Engl J Med 2008, **359**：2396-2398

松山高明　Matsuyama Taka-aki

*国立循環器病研究センター臨床検査部 臨床病理科

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REVIEW

Incretin Therapy and Heart Failure

Jun-ichi Oyama, MD, PhD; Koichi Node, MD, PhD

Type 2 diabetes mellitus (T2DM) is widely prevalent and a critical risk factor for cardiovascular disease that increases both morbidity and mortality. Recently, new therapies based on the actions of the incretin hormones have become widely used, offering advantages over conventional treatments by limiting hypoglycemia and achieving glycemic control. Moreover, many experimental studies have suggested that GLP-1 and related drugs exert cardioprotective effects on atherosclerosis and cardiac dysfunction both in vitro and in vivo. However, there is thus far little clinical evidence supporting the efficacy of incretin therapy in patients with cardiovascular disease. This review focuses on the effects of GLP-1-related therapy on cardiac function from the bench to the bed, with a discussion of possible underlying mechanisms.

Key Words: DPP-4 inhibitor; GLP-1; Heart failure; Incretin; Type 2 diabetes mellitus (T2DM)

Type 2 diabetes (T2DM) is one of the most important risk factors for the development of cardiovascular disease, as it promotes both systemic atherosclerosis and lifestyle-associated diseases. Incretin-based therapies, including treatment with glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists and dipeptidyl peptidase (DPP)-4 inhibitors, have become widely used as a new class of antidiabetic drugs that exhibit different mechanisms of action from those of conventional antidiabetic agents. Incretin hormones depend on blood glucose to stimulate insulin. Because the use of DPP-4 inhibitors is associated with a lower incidence of hypoglycemia than is observed with conventional hypoglycemic drugs, they potentially improve the mortality rate of patients with T2DM by achieving strict glycemic control without causing fatal hypoglycemia. The GLP-1R has been detected in coronary endothelial cells, coronary smooth muscle cells, cardiomyocytes and human umbilical vein endothelial cells, as well as monocytes and macrophages.[1–4] Interestingly, GLP-1 acts on multiple organs, not simply the pancreas, including the heart and vasculature (**Figure 1**). Therefore, GLP-1-related therapy exerts effects on the cardiovascular system, and recent evidence suggests that GLP-1-related treatment has potent pleiotropic beneficial effects on cardiovascular risk factors, beyond its effects on glycemic control. This review focuses on the theoretical and practical effects of incretin-related therapy on cardiac function, with a description of possible mechanism(s) of action.

Biology of Incretins

Incretin hormones are secreted from the gastrointestinal tract in response to food intake and have several systemic effects, including glucose-dependent stimulation of insulin secretion by pancreatic beta cells. Two incretins have been identified: GLP-1, which is derived from the L cells of the distal small intestine and large bowel, and glucose-dependent insulinotropic polypeptide (GIP), which is derived from the K cells of the proximal small intestine. GLP-1 and GIP are glucose-lowering agents that can interfere with postprandial hyperglycemia, which has been demonstrated as associated with cardiovascular complications. The biologically active forms of GLP-1 include GLP-1(7-37) and GLP-1(7-36)amide. These peptides arise from the selective cleavage of the proglucagon molecule. GLP-1(7-36)amide is abundant in the circulation after meals and stimulates insulin secretion by interacting with the GLP-1 receptors on pancreatic beta cells. DPP-4 degrades GLP-1(7-36)amide to inactive GLP-1(9-36)amide, and DPP-4 inhibitors bind to DPP-4 to prevent the breakdown of GLP-1 and GIP,[5] thereby increasing the half-life and bioavailability of active incretins, ultimately enhancing their physiological effects. GLP-1(7-36)amide has been widely studied for its role as an active incretin and is referred to as GLP-1, unless otherwise specified. GLP-1(9-36) amide is thought to be an inactive metabolite because of its 1,000-fold lower affinity for GLP-1R and action as a weak competitive antagonist without incretin activity at pharmacological doses. However, GLP-1(9-36)amide may have potent effects on the cardiovascular system, similar to GLP-1(7-36) amide. Although it remains controversial, GLP-1 may undergo multiple cycles of enzymatic degradation by DPP-4 and neprilysin. Therefore, the precise biological pathways of GLP-1 and related enzymes and the roles of metabolites in each step of the process in vivo need to be elucidated in the near future.

Effects of Incretins on Cardiac Function

Cardiomyocytes in Vitro

GLP-1 rapidly increases the 3'-5'-cyclic adenosine monophosphate (cAMP) levels in adult rat ventricular cardiac myocytes, consistent with its effect on pancreatic beta cells, in a manner

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Departments of Advanced Cardiology (J.O.), Cardiovascular Medicine (K.N.), Saga University Faculty of Medicine, Saga, Japan
Mailing address: Jun-ichi Oyama, Department of Advanced Cardiology, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan. E-mail: junoyama@cc.saga -u.ac.jp
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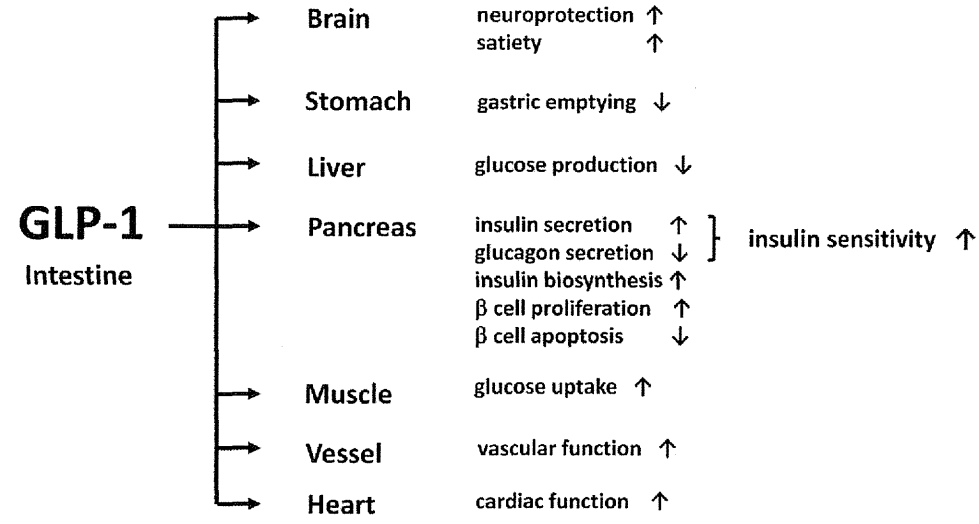

Figure 1. Schema of the physiological effects of glucagon-like peptide-1 (GLP-1) on various organs.

that is not coupled with an increase in the intracellular Ca^{2+} concentration or subsequent cardiomyocyte contractility, as would be expected for cAMP-generating agents in the heart.[6] Liraglutide increases cAMP formation and reduces caspase-3 activation in murine cardiomyocytes in a GLP-1R-dependent manner in vitro.[7] Therefore, GLP-1R activation in primary cultures of cardiomyocytes increases the cAMP content in association with anti-apoptotic properties.

In Vivo and ex Vivo Experimental Data

GLP-1R knockout mice exhibit a reduced resting heart rate (HR), elevated left ventricular end-diastolic pressure (LVEDP) and increased LV thickness because of impaired LV contractility and diastolic dysfunction, as compared with wild-type mice.[8] Conversely, GLP-1R preserves the HR and LV thickness and normally lowers the LVEDP.

Model of Myocardial Ischemia-Reperfusion (IR) and Infarction (MI)

GLP-1 and its related therapy have been demonstrated to inhibit the activation of cell death mechanisms in several experimental models of myocardial IR and MI.

GLP-1 has also been demonstrated to exert beneficial effects on cardiac function via downregulation of inflammatory cells activated by MI.[9,10] In addition, GLP-1 enhances LV function by myocardial glucose uptake in the postischemic myocardium through an increase in the expression of glucose transporter (GLUT)-1 and -4 in the myocardium in association with increased p38 α MAP kinase activity, eNOS expression and myocardial NO uptake, although GLP-1 changes neither the myocardium adenylyl cyclase activity nor the level of Akt phosphorylation, known insulin-dependent signaling pathways for glucose uptake.[7,11,12]

GLP-1 and the GLP-1(9-36) metabolite also improve myocardial contractility and coronary blood flow following ischemia in a mouse perfused heart model.[4] GLP-1 directly protects the heart against myocardial IR injury and reduces the activation of the pro-apoptotic protein, Bad, as well as the infarct size in isolated perfused rat hearts and animal models of IR; these effects are abolished in the hearts in vitro by GLP-1R antagonists, cAMP inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors and p42/44 mitogen-activated protein kinase inhibitors.[13] DPP-4-resistant GLP-1 analogs fused to non-glycosylated human transferrin possess anti-apoptotic properties accompanied by a reduction in the infarct size and improvements in wall motion abnormalities and the ejection fraction (EF) in a model of myocardial IR in rabbits.[14] The infusion of GLP-1 or the exenatide analog at 2 weeks after coronary ligation significantly increases the LVEF, while also reducing the incidence of adverse LV remodeling and improving survival.[15] Exenatide reduces the infarct size and reactive oxygen species (ROS) production and inhibits caspase-3 expression and DNA fragmentation in a porcine model of myocardial IR injury.[16] Similarly, treatment with liraglutide for 1 week prior to coronary ligation in mice reduces both the frequency of cardiac rupture and the infarct size, and increases the cardiac output (CO) and survival rate via the inhibition of caspase-3 activation in cardiomyocytes.[7] Furthermore, albiglutide therapy preserves myocardial viability and reduces the production of lactate after IR injury in the rat heart.[17]

The genetic deletion or chemical inhibition of DPP-4 in mice improves their cardiac function after MI by activating cell survival signaling, including that of phosphorylated Akt and pGSK3β.[18] Combined treatment of mice with granulocyte colony-stimulating factor and a DPP-4 inhibitor preserves cardiac function via enhanced stem cell mobilization and cardiomyocyte regeneration after MI.[19]

In summary, a number of findings suggest that the cardioprotective effects of incretins in IR models are mediated by: (1) reductions in the number of inflammatory cells,[9,10] (2) improvements in myocardial circulation,[10] (3) increases in the level of myocardial glucose uptake in order to stimulate more efficient ATP production,[7,11,12,17] and (4) activation of reperfusion injury signaling kinase (RISK) pathway kinases, such as PI3K, ERK1/2, cAMP, PKA, Akt and P70S6K,[7,18,20-26] as PI3K activation results in myocardial protection in the setting of IR injury.[27]

Table. Clinical Studies of Cardiac Function in Patients Treated With GLP-1 and GLP-1-Related Therapies

Author	Pathology	Therapy	Results
Nikokaidis et al[28]	AMI with PCI vs. healthy subjects	GLP-1	EF ↑
Lønborg et al[34]	AMI with PCI	Exenatide	Myocardial salvage index ↑
Sokos GG et al[35]	CAD with CABG	GLP-1	EF→ Arrhythmia ↓
Read et al[36]	CAD	Sitagliptin vs. placebo	Myocardial stunning ↓ EF ↑
Sokos et al[37]	Heart failure	GLP-1	EF ↑
Halbirk et al[38]	Heart failure	GLP-1	HR ↑, DBP ↑ EF, BNP→
Trainsdottir et al[39]	T2DM with heart failure	Recombinant GLP-1	Trend in cardiac function ↑
Gutzwiller et al[42]	Obese vs. healthy subjects	GLP-1	Natriuresis ↑

AMI, acute myocardial infarction; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; DBP, diastolic blood pressure; EF, ejection fraction; GLP-1; glucagon-like peptide-1; HF, heart failure; PCI, percutaneous coronary intervention.

Model of HF

Studies using animal models have demonstrated that GLP-1R activation-independent actions via the effects of GLP-1R may have a beneficial impact on the failing heart. In dogs with pacing-induced dilated cardiomyopathy (DCM), the infusion of recombinant GLP-1, GLP-1 (7-36) and GLP-1 (9-36) increases the myocardial glucose uptake and insulin sensitivity, improves LV function, stroke volume (SV) and CO, enhances cardiac insulin sensitivity and the LV dP/dt values and decreases the LVEDP, HR and systemic vascular resistance.[28,29] Moreover, GLP-1 decreases the HR and increases LV systolic function, in addition to reducing the plasma levels of norepinephrine and glucagon. In spontaneously hypertensive and HF-prone rats, GLP-1 treatment for 3 months improves the survival rate and preserves LV contractility in association with reduced cardiomyocyte apoptosis.[30] The administration of sitagliptin for 3 weeks to nondiabetic pigs with pacing-induced DCM results in a reduced HR, increased SV and preserved renal function.[31] However, the administration of vildagliptin to nondiabetic rats before or after coronary ligation has no beneficial effects on either LV function or cardiac gene expression.[32] Sitagliptin therapy in db/db mice reduces AMPK and acetyl CoA carboxylase phosphorylation, as well as CD36 expression in the sarcolemmal membrane of the myocardium, suggesting that DPP-4 inhibition reduces myocardial fatty acid (FA) uptake and subsequent metabolism.[33] However, treatment with sitagliptin does not improve systolic function in db/db mice, although it reduces the degree of myocardial fibrosis and improves the LV relaxation constant in association with improved diastolic function, in addition to reducing myocardial p53 expression and apoptosis of cardiomyocytes.

Clinical Investigation of Human Cardiac Function (Table)

GLP-1 has been cited as improving myocardial function in T2DM patients with MI and/or HF. In patients with a low level of LV dysfunction after MI or PCI, infusion of GLP-1 results in an improvement of both the LVEF and wall motion.[28,34] A randomized study assessing the effect of continuous GLP-1 infusion in 20 patients undergoing coronary artery bypass grafting documented improved glycemic control, reduced frequency of inotropic and vasoactive infusions, and a lower incidence of arrhythmias in the GLP-1-treated patients.[35] Treatment with sitagliptin was found to improve dobutamine-induced regional wall motion abnormalities in ischemic segments on stress echocardiography and attenuate postischemic stunning in 14 patients with coronary artery disease (CAD) and preserved global LV function.[36] Sokos et al demonstrated in a single-center nonrandomized trial that a continuous infusion of GLP-1 for 5 weeks in 12 patients with HF (New York Heart Association (NYHA) class III/IV) with or without T2DM improved the LVEF, oxygen consumption, 6-min walk test scores and quality of life, even in the nondiabetic patients.[37] However, Halbirk et al reported that infusion of GLP-1 for 48 h in 15 nondiabetic patients with stable CHF (LVEF <40% and NYHA class II–III) and HF reduced the blood glucose levels and increased the plasma insulin levels, although it had no significant effect on LV function, with only modest increases in HR and diastolic blood pressure (BP), in a double-blind placebo-controlled crossover design.[38] Trainsdottir et al demonstrated a beneficial trend in cardiac function in patients with T2DM and HF after infusion of recombinant GLP-1.[39] A short duration of infusion of GLP-1 may be insufficient to treat a decompensated failing heart.

Other Possible Effects of Incretins on Cardiovascular Risk Factors

Lowering BP and Improving Endothelial Function

In recent studies, DPP-4 inhibitors and GLP-1 analogs have been recognized as lowering systemic BP.[40,41] A possible mechanism underlying this effect is the extraction of Na^+, as GLP-1 induces natriuresis in humans.[42]

For diabetic vascular and endothelial injury,[43] substantial data exist regarding the beneficial effects of GLP-1 and related drugs on endothelial function and the incidence of atherosclerosis, including (1) increasing the eNOS expression,[44,45] (2) increasing the number of endothelial progenitor cells (EPCs),[46] (3) decreasing the number of inflammatory cells and ROS production,[47] and (4) reducing the adhesion and activation of macrophages,[1,48] although these mechanisms cannot be described in detail in this review. Nevertheless, improved myocardial perfusion following the recovery of endothelial function may contribute to myocardial contractility. In addition, the incremental activity of eNOS may reduce BP, as increased BP is recognized by genetic deletion or pharmacological inhibition of NOS in vivo.[49,50] Indeed,

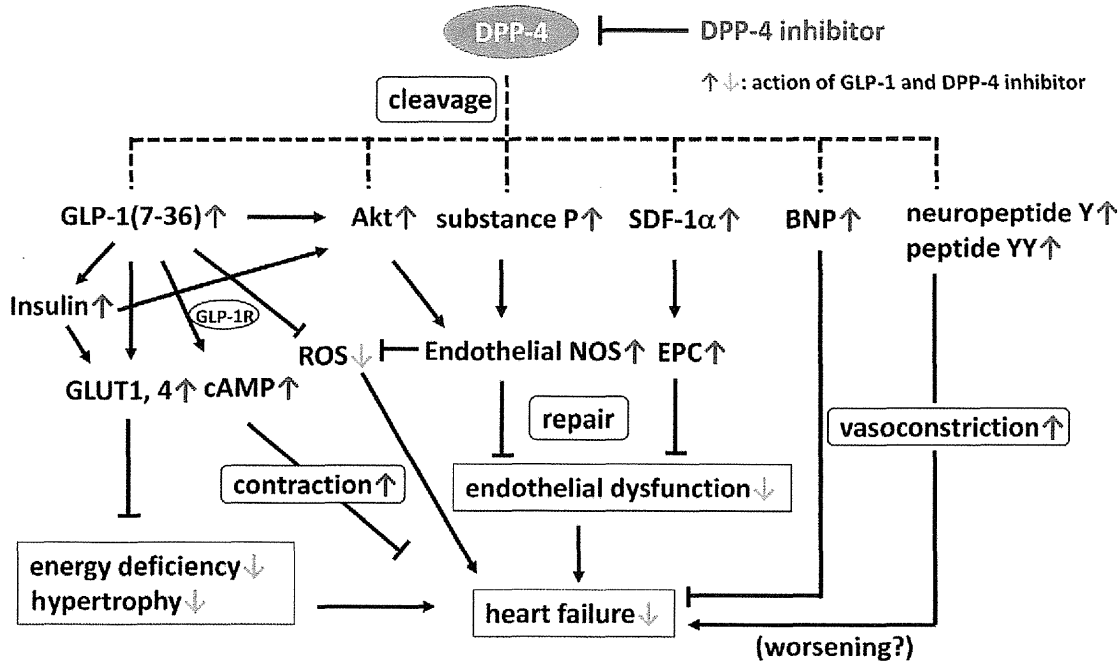

Figure 2. Possible mechanisms underlying the beneficial effects of incretins on the failing heart. In addition to the effects of GLP-1, DPP-4 cleaves a wide variety of substrates, DPP-4 inhibition keep the biological active forms of substrates and have many possible functions on cardiovascular system (red arrow). BNP, brain natriuretic peptide; DPP, dipeptidyl peptidase; EPC, endothelial progenitor cell; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; NOS, nitric oxide synthase; ROS, reactive oxygen species; SDF-1, stromal cell-derived factor-1.

sitagliptin improves endothelial function and reduces inflammation in patients with T2DM and CAD.[51]

Shift of Cardiac Metabolism in the Failing Heart

Alterations in myocardial substrate preference from FA to glucose are recognized in the failing heart. It may be substitutional. Therefore, insulin resistance with reduced GLUT-4 expression and increased levels of insulin are recognized in patients with HF.[52] Although it is controversial whether myocardial glucose uptake is increased or not in the failing heart, DPP-4 inhibition or GLP-1 upregulate GLUT4 expression, and regulation of cardiac metabolism can be a therapeutic target for incretin therapy.[53,54]

Possible Original Effects of DPP-4 Inhibitors

In contrast to GLP-1 and GLP-1 receptor agonists, DPP-4 inhibitors inhibit DPP-4 throughout the body. As DPP-4 cleaves a wide variety of substrates, including stromal cell-derived factor-1 (SDF-1) alpha, which stimulates the bone marrow mobilization of EPCs and B-type natriuretic peptide (BNP) (1–32), the active form of BNP,[55] DPP-4 inhibition repairs endothelial cells and improves cardiac function, thus resulting in an indirect improvement in endothelial function. Neuropeptide Y (NPY) and peptide YY (PYY) are also targets for cleavage by DPP-4. As both these peptides induce vasoconstriction through Y(1) receptors, inhibition of DPP-4 may result in vasoconstriction.[56] Although it remains uncertain, NPY and its substrates appear to influence the cardiovascular system. These findings are promising, and the precise biological role of DPP-4 in the cardiovascular system requires further investigation. Figure 2 summarized the possible mechanisms underlying GLP-1 and DPP-4 inhibition in the failing heart.

Incretins and Cardiovascular Outcomes

Do Incretins Really Improve Mortality From Cardiovascular Disease?

Recently, the results of cardiovascular safety trials T2DM drugs (EXAMINE trial with alogliptin[57] and SAVOR-TIMI 53 trial with saxagliptin[58]) were reported. These studies found no effect on the risk of fatal or nonfatal cardiac events and no increases in the risk of pancreatitis or pancreatic cancer. Although this is good news for users of these drugs, the results were disappointing because the studies did not demonstrate any cardiovascular protective benefits of DPP-4 inhibitors. On the other hand, the follow-up period was too short to evaluate the incidence of cardiovascular events, as the effects of drugs in combating proatherosclerotic processes in patients with diabetes mellitus usually requires more than 10 years. In the SAVOR-TIMI 53 trial, more patients were hospitalized for HF in the saxagliptin group than in the placebo group. These results are unexpected and should be considered within the context of multiple testing, which may have produced false-positive findings. The results of further subanalyses and other ongoing trials are waited. The relatively small HbA_{1c}-lowering effects of saxagliptin and alogliptin observed in the SAVOR and EXAMINE trials, averaging only 0.3–0.4 percentage points, must be also discussed. However, the effect of adequate glycemic control without severe hypoglycemia is irreplaceable for those with T2DM. Currently, new, safe tools are available for the treatment of T2DM. How-

ever, new drugs require outrageous costs nowadays and both doctors and patients expect excessive benefits beyond conventional ones. Further studies must be conducted dispassionately as to whether incretin-related drugs have beneficial effects on prognosis, including the incidence of cardiovascular events, in humans.

Conclusions

Atherosclerosis and subsequent cardiovascular disease are often fatal, and providing early preventive care for cardiovascular complications by ensuring strict glucose control is essential for patients with T2DM.[59] Although the final answer remains uncertain, the current findings add to a growing body of evidence suggesting that we may be entering a new era of cardiovascular diabetology with the development of new drugs. Ongoing randomized prospective clinical studies will provide more solid evidence regarding the long-term clinical effects of GLP-1-related therapies in patients with T2DM with a high risk of cardiovascular disease.

Conflict of Interest Statement

J.O. belongs to the endowed department by Fukuda Denshi Co, Ltd. K.N. received remuneration including lecture fees from AstraZeneca, Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Pfizer Inc, MSD K.K., Daiichi Sankyo Company, Ltd, Kowa Pharmaceutical Co, Ltd, Takeda Pharmaceutical Co, Ltd, Novartis Pharmaceuticals Japan, Mitsubishi Tanabe Pharma Corporation, and Dainippon Sumitomo Pharma Co, Ltd. K.N also received scholarship funds or donations granted by Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Daiichi Sankyo Company, Ltd, Takeda Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, and MSD K.K.

References

1. Arakawa M, Mita T, Azuma K, Ebato C, Goto H, Nomiyama T, et al. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010; **59:** 1030–1037.
2. Nyström T, Gutniak MK, Zhang Q, Zhang F, Holst JJ, Ahrén B, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *Am J Physiol Endocrinol Metab* 2004; **287:** E1209–E1215.
3. Ishibashi Y, Matsui T, Takeuchi M, Yamagishi S. Glucagon-like peptide-1 (GLP-1) inhibits advanced glycation end product (AGE)-induced up-regulation of VCAM-1 mRNA levels in endothelial cells by suppressing AGE receptor (RAGE) expression. *Biochem Biophys Res Commun* 2010; **391:** 1405–1408.
4. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation* 2008; **117:** 2340–2350.
5. Gallwitz B. Review of sitagliptin phosphate: A novel treatment for type 2 diabetes. *Vasc Health Risk Manag* 2007; **3:** 203–210.
6. Vila Petroff MG, Egan JM, Wang X, Sollott SJ. Glucagon-like peptide-1 increases cAMP but fails to augment contraction in adult rat cardiac myocytes. *Circ Res* 2011; **89:** 445–452.
7. Noyan-Ashraf MH, Momen MA, Ban K, Sadi AM, Zhou YQ, Riazi AM, et al. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009; **58:** 975–983.
8. Gros R, You X, Baggio LL, Kabir MG, Sadi AM, Mungrue IN, et al. Cardiac function in mice lacking the glucagon-like peptide-1 receptor. *Endocrinology* 2003; **144:** 2242–2252.
9. Dokken BB, La Bonte LR, Davis-Gorman G, Teachey MK, Seaver N, McDonagh PF. Glucagon-like peptide-1 (GLP-1), immediately prior to reperfusion, decreases neutrophil activation and reduces myocardial infarct size in rodents. *Horm Metab Res* 2011; **43:** 300–305.
10. Dokken BB, Hilwig WR, Teachey MK, Panchal RA, Hubner K, Allen D, et al. Glucagon-like peptide-1 (GLP-1) attenuates post-resuscitation myocardial microcirculatory dysfunction. *Resuscitation* 2010; **81:** 755–760.
11. Zhao T, Parikh P, Bhashyam S, Bolukoglu H, Poornima I, Shen YT, et al. Direct effects of glucagon-like peptide-1 on myocardial contractility and glucose uptake in normal and postischemic isolated rat hearts. *J Pharmacol Exp Ther* 2006; **317:** 1106–1113.
12. Bhashyam S, Fields AV, Patterson B, Testani JM, Chen L, Shen YT, et al. Glucagon-like peptide-1 increases myocardial glucose uptake via p38alpha MAP kinase-mediated, nitric oxide-dependent mechanisms in conscious dogs with dilated cardiomyopathy. *Circ Heart Fail* 2010; **3:** 512–521.
13. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 2005; **54:** 146–151.
14. Matsubara M, Kanemoto S, Leshnower BG, Albone EF, Hinmon R, Plappert T, et al. Single dose GLP-1-Tf ameliorates myocardial ischemia/reperfusion injury. *J Surg Res* 2011; **165:** 38–45.
15. Liu Q, Anderson C, Broyde A, Polizzi C, Fernandez R, Baron A, et al. Glucagon-like peptide-1 and the exenatide analogue AC3174 improve cardiac function, cardiac remodeling, and survival in rats with chronic heart failure. *Cardiovasc Diabetol* 2010; **9:** 76.
16. Timmers L, Henriques JP, de Kleijn DP, Devries JH, Kemperman H, Steendijk P, et al. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. *J Am Coll Cardiol* 2009; **53:** 501–510.
17. Bao W, Aravindhan K, Alsaid H, Chendrimada T, Szapacs M, Citerone DR, et al. Albiglutide, a long lasting glucagon-like peptide-1 analog, protects the rat heart against ischemia/reperfusion injury: Evidence for improving cardiac metabolic efficiency. *PLoS One* 2011; **6:** e23570, doi:10.1371/journal.pone.0023570.
18. Sauve M, Ban K, Momen MA, Zhou YQ, Henkelman RM, Husain M, et al. Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice. *Diabetes* 2010; **59:** 1063–1073.
19. Zaruba MM, Zhu W, Soonpaa MH, Reuter S, Franz WM, Field LJ. Granulocyte colony-stimulating factor treatment plus dipeptidyl-peptidase-IV inhibition augments myocardial regeneration in mice expressing cyclin D2 in adult cardiomyocytes. *Eur Heart J* 2012; **33:** 129–137.
20. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 2005; **54:** 146–151.
21. Ku HC, Chen WP, Su MJ. DPP4 deficiency preserves cardiac function via GLP-1 signaling in rats subjected to myocardial ischemia/reperfusion. *Naunyn Schmiedebergs Arch Pharmacol* 2011; **384:** 197–207.
22. Iwasa M, Yamada Y, Kobayashi H, Yasuda S, Kawamura I, Sumi S, et al. Both stimulation of GLP-1 receptors and inhibition of glycogenolysis additively contribute to a protective effect of oral miglitol against ischaemia-reperfusion injury in rabbits. *Br J Pharmacol* 2011; **164:** 119–131.
23. Bose AK, Mocanu MM, Carr RD, Yellon DM. Myocardial ischaemia-reperfusion injury is attenuated by intact glucagon like peptide-1 (GLP-1) in the in vitro rat heart and may involve the p70s6K pathway. *Cardiovasc Drugs Ther* 2007; **21:** 253–256.
24. Ye Y, Keyes KT, Zhang C, Perez-Polo JR, Lin Y, Birnbaum Y. The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective effect of pioglitazone is partially dependent on PKA. *Am J Physiol Heart Circ Physiol* 2010; **298:** H1454–H1465.
25. Huisamen B, Genade S, Lochner A. Signalling pathways activated by glucagon-like peptide-1 (7-36) amide in the rat heart and their role in protection against ischaemia. *Cardiovasc J Afr* 2008; **19:** 77–83.
26. Huisamen B, Genis A, Marais E, Lochner A. Pre-treatment with a DPP-4 inhibitor is infarct sparing in hearts from obese, pre-diabetic rats. *Cardiovasc Drugs Ther* 2011; **25:** 13–20.
27. Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: Targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* 2004; **61:** 448–460.
28. Nikolaidis LA, Elahi D, Hentosz T, Doverspike A, Huerbin R, Zourelias L, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing induced dilated cardiomyopathy. *Circulation* 2004; **110:** 955–961.
29. Nikolaidis LA, Elahi D, Shen YT, Shannon RP. Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2005; **298:** H2401–H2408.
30. Poornima I, Brown SB, Bhashyam S, Parikh P, Bolukoglu H, Shannon RP. Chronic glucagon-like peptide-1 infusion sustains left ventricular systolic function and prolongs survival in the spontaneously hypertensive, heart failure-prone rat. *Circ Heart Fail* 2008; **1:** 153–160.
31. Gomez N, Touihri K, Matheeussen V, Mendes Da Costa A, Mahmoudabady M, Mathieu M, et al. Dipeptidyl peptidase IV inhibition improves cardiorenal function in overpacing-induced heart fail-

ure. *Eur J Heart Fail* 2012; **14:** 14–21.
32. Yin M, Silljé HH, Meissner M, van Gilst WH, de Boer RA. Early and late effects of the DPP-4 inhibitor vildagliptin in a rat model of post-myocardial infarction heart failure. *Cardiovasc Diabetol* 2011; **10:** 85.
33. Lenski M, Kazakov A, Marx N, Böhm M, Laufs U. Effects of DPP-4 inhibition on cardiac metabolism and function in mice. *J Mol Cell Cardiol* 2011; **51:** 906–918.
34. Lønborg J, Vejlstrup N, Kelbæk H, Bøtker HE, Kim WY, Mathiasen AB, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012; **33:** 1491–1499.
35. Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ Jr, Maher TD, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. *Am J Cardiol* 2007; **100:** 824–829.
36. Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. *Circ Cardiovasc Imaging* 2010; **3:** 195–201.
37. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006; **12:** 694–699.
38. Halbirk M, Nørrelund H, Møller N, Holst JJ, Schmitz O, Nielsen R, et al. Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure. *Am J Physiol Heart Circ Physiol* 2010; **298:** H1096–H1102.
39. Thrainsdottir I, Malmberg K, Olsson A, Gutniak M, Rydén L. Initial experience with GLP-1 treatment on metabolic control and myocardial function in patients with type 2 diabetes mellitus and heart failure. *Diab Vasc Dis Res* 2004; **1:** 40–43.
40. Sakamoto Y, Oyama J, Ikeda H, Kuroki S, Gondo S, Iwamoto T, et al; S-DOG investigators. Effects of sitagliptin beyond glycemic control: Focus on quality of life. *Cardiovasc Diabetol* 2013; **12:** 35.
41. Scheen AJ. Cardiovascular effects of gliptins. *Nat Rev Cardiol* 2013; **10:** 73–84.
42. Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab* 2004; **89:** 3055–3061.
43. Gilbert RE. Endothelial loss and repair in the vascular complications of diabetes. *Circ J* 2013; **77:** 849–856.
44. Ding L, Zhang J. Glucagon-like peptide-1 activates endothelial nitric oxide synthase in human umbilical vein endothelial cells. *Acta Pharmacol Sin* 2012; **33:** 75–81.
45. Erdogdu O, Nathanson D, Sjöholm A, Nyström T, Zhang Q. Exendin-4 stimulates proliferation of human coronary artery endothelial cells through eNOS-, PKA- and PI3K/Akt-dependent pathways and requires GLP-1 receptor. *Mol Cell Endocrinol* 2010; **325:** 26–35.
46. Xiao-Yun X, Zhao-Hui M, Ke C, Hong-Hui H, Yan-Hong X. Glucagon-like peptide-1 improves proliferation and differentiation of endothelial progenitor cells via upregulating VEGF generation. *Med Sci Monit* 2011; **17:** BR35–BR41.
47. Shiraki A, Oyama J, Komoda H, Asaka M, Komatsu A, Sakuma M, et al. The glucagon-like peptide 1 analog liraglutide reduces TNF-α-induced oxidative stress and inflammation in endothelial cells. *Atherosclerosis* 2012; **221:** 375–382.
48. Gaspari T, Liu H, Welungoda I, Hu Y, Widdop RE, Knudsen LB, et al. A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE-/- mouse model. *Diab Vasc Dis Res* 2011; **8:** 117–124.
49. Huang PL, Huang Z, Mashimo H, Block KD, Moskowitz MA, Bevan JA, et al. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature* 1995; **377:** 239–242.
50. Rees DD, Palmer RM, Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. *Proc Natl Acad Sci USA* 1989; **86:** 3375–3378.
51. Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, et al. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. *Circ J* 2013; **77:** 1337–1344.
52. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005; **85:** 1093–1129.
53. Green CJ, Henriksen TI, Pedersen BK, Solomon TP. Glucagon like peptide-1-induced glucose metabolism in differentiated human muscle satellite cells is attenuated by hyperglycemia. *PLoS One* 2012; **7:** e44284, doi:10.1371/journal.pone.0044284.
54. Giannocco G, Oliveira KC, Crajoinas RO, Venturini G, Salles TA, Fonseca-Alaniz MH, et al. Dipeptidyl peptidase IV inhibition upregulates GLUT4 translocation and expression in heart and skeletal muscle of spontaneously hypertensive rats. *Eur J Pharmacol* 2013; **698:** 74–86.
55. Vanderheyden M, Bartunek J, Goethals M, Verstreken S, Lambeir AM, De Meester I, et al. Dipeptidyl-peptidase IV and B-type natriuretic peptide. From bench to bedside. *Clin Chem Lab Med* 2009; **47:** 248–252.
56. Jackson EK, Zhang M, Liu W, Mi Z. Inhibition of renal dipeptidyl peptidase IV enhances peptide YY1-36-induced potentiation of angiotensin II-mediated renal vasoconstriction in spontaneously hypertensive rats. *J Pharmacol Exp Ther* 2007; **323:** 431–437.
57. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013; **369:** 1327–1335.
58. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013; **369:** 1317–1326.
59. Koshizaka M, Green JB, Alexander JH. Glycemic Management in Glycemic management in diabetes and the associated cardiovascular risk: Are we helping or hurting our patients? *Circ J* 2012; **76:** 1572–1580.