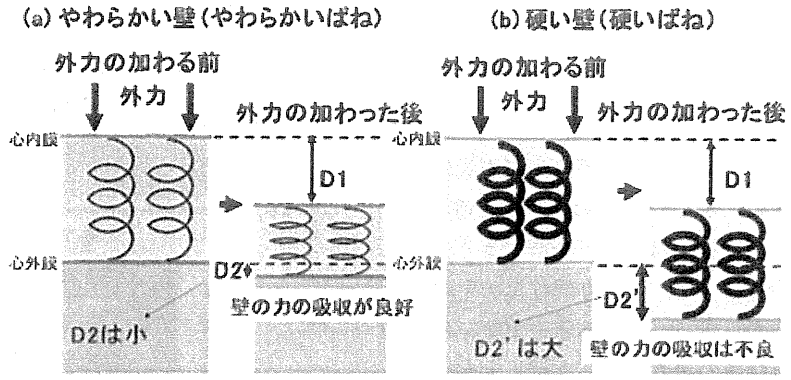

Fig. 7 線形弾性理論．**a** やわらかい壁の場合．**b** 硬い壁の場合（文献 16 より引用，改変）．心内膜面の移動距離 D1 が等しい場合でも，D2'＞D2 となる

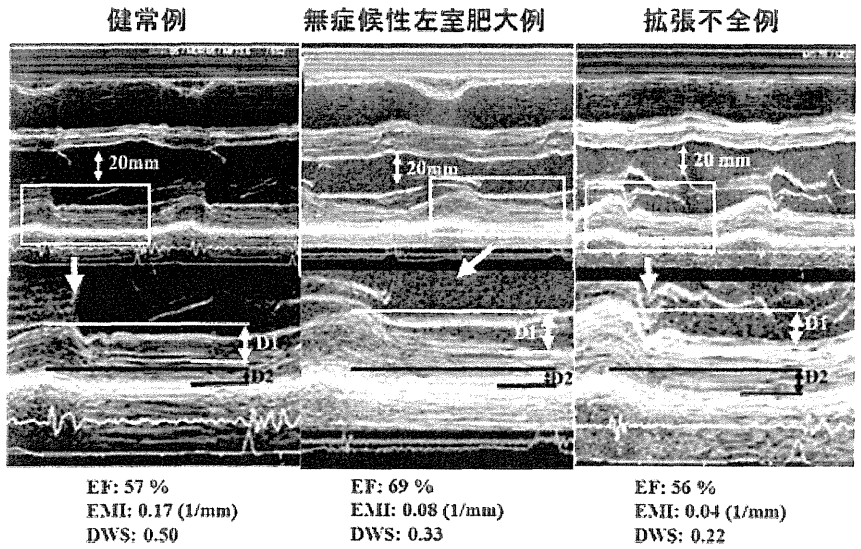

Fig. 8 健常例，無症候性左室肥大例，拡張不全例における左室 M モード図の典型例（文献 16 より引用，改変）．各患者は拡張期における左室心内膜面の動き（D1）は同様であるが，左室心外膜面の動き（D2）は拡張不全患者で大きく，EMI および DWS は拡張不全患者で最も低値を呈した

わらかい左室壁では拡張期の左室壁心外膜面の動きは小さく，硬い左室壁では大となる（**Fig. 8**）．つまり，心周期を通じた左室壁厚の変化がやわらかい左室壁では大となり，硬い左室壁では小となる．我々は，この原理をもとに epicardial movement index（EMI）：

$$\frac{\text{拡張期心内膜面の移動距離} - \text{拡張期心外膜面の移動距離}}{\text{拡張開始時の左室壁厚} \times \text{拡張期心外膜面の移動距離}}$$

を考案し，EMI が心筋スティフネス係数と有意な負の相関を示し，前負荷の影響を受けにくいことを確認した[16]．EMI の分子の（拡張期心内膜面の移動距離－拡張期心外膜面の移動距離）は（収縮末期壁厚－拡張末期壁厚）と等しく，拡張開始時の左室壁厚は収縮末期壁厚に該当する．EMI を簡略化した指標である Diastolic wall strain（DWS）：

$$\frac{\text{収縮末期壁厚} - \text{拡張末期壁厚}}{\text{収縮末期壁厚}}$$

も心筋スティフネス係数と有意な負の相関関係にある[16]．EMI も DWS も wall thinning，wall thickening に該当する要素が含まれているが，いずれも左室内径短縮率，peak ＋dP/dt など左室収縮性を示す指標と相関しない．

我々は本指標の臨床的有用性を検討するため左室駆出率が保持された糖尿病患者において心不全発症

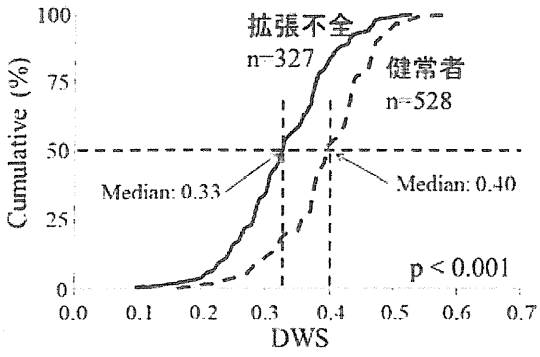

Fig. 9 健常例，拡張不全例における DWS の分布の相違．健常例における DWS の中間値は 0.40，拡張不全例では 0.33 であった（文献 18 より引用，改変）

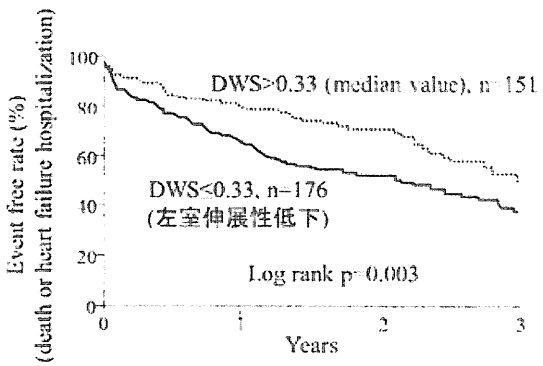

Fig. 10 拡張不全例における DWS と予後の関係．DWS が中間値（**Fig. 9** 参照）より低値の症例では，予後はさらに不良であった（文献 18 より引用，改変）

リスク因子を検討したところ，左室重量係数や e' ではなく DWS 低値が女性，肥満，貧血とともに選択された[17]．さらに，米国 Mayo Clinic との共同研究において健常例と拡張不全患者における DWS の分布の相違（**Fig. 9**）を明らかにすると同時に，拡張不全患者では DWS 低値であれば予後がより不良であり，DWS は年齢，性，E/e'，左室重量係数，肺動脈圧，血中 B タイプナトリウム利尿ペプチド濃度とは独立した予後規定因子であることを示した（**Fig. 10**）[18]．つまり，理論的に左室スティフネス亢進を反映していると考えられる DWS の低下は，拡張不全発症のリスクであると同時に，拡張不全発症後の予後不良サインでもある．DWS は心エコー法に限らず computed tomography や magnetic resonance imaging などの左室壁厚を測定できる画像診断法であれば求めることができ，今後の臨床現場での幅広い応用が期待される．

11. 心房細動患者ではどのように考えるべきか

ここまでの記載は洞調律の患者についてである．心不全患者の 30－40％では心房細動を合併している．また，心不全発症率の高い高齢者になるほど心房細動発症率が上昇し，70 歳を超えると 20 名に 1 名，80 歳を超えると 10 名に 1 名が発症する．現在のところ心房細動患者における拡張機能評価法として広く受け入れられているものはない．我々が肺がん患者を対象として術後の心房細動発症と術前の心エコー指標との関係を検討したところ，心房細動発症患者は術前の E/e' が高値であった[19]．したがって，拡張機能障害が心房細動発症の大きなリスクであり，心房細動の存在そのものが拡張機能障害の存在を示しているとも考えられ，欧州心臓病学会の拡張不全診断フローチャートでは，心房細動の存在は左室肥大の存在とならび，拡張機能障害を示す所見として扱われている[20]．

12. おわりに

拡張機能は心不全の病態を規定する重要な因子の一つであるが，収縮機能を評価する際の左室駆出率のような単純で可視的な指標が存在しないため臨床現場で評価を行うことが容易ではない．このため拡張機能が病態形成に及ぼす影響も過小評価されがちである．超高齢化社会に突入した我国では拡張不全患者の増加が懸念されており，拡張不全を含む心不全診療の向上のためには，拡張機能評価法の確立に向けたさらなる研究の進展が望まれる．

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アンチエイジングから拡張不全を考える

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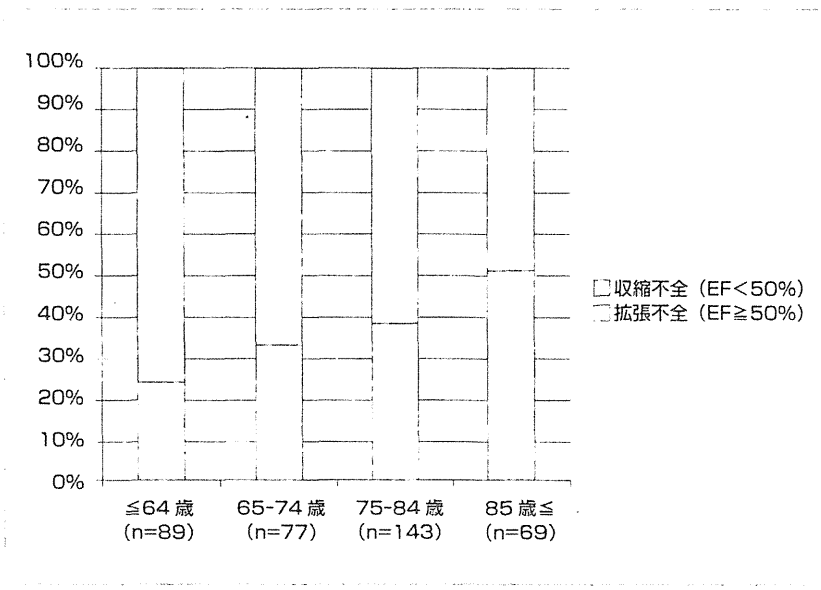
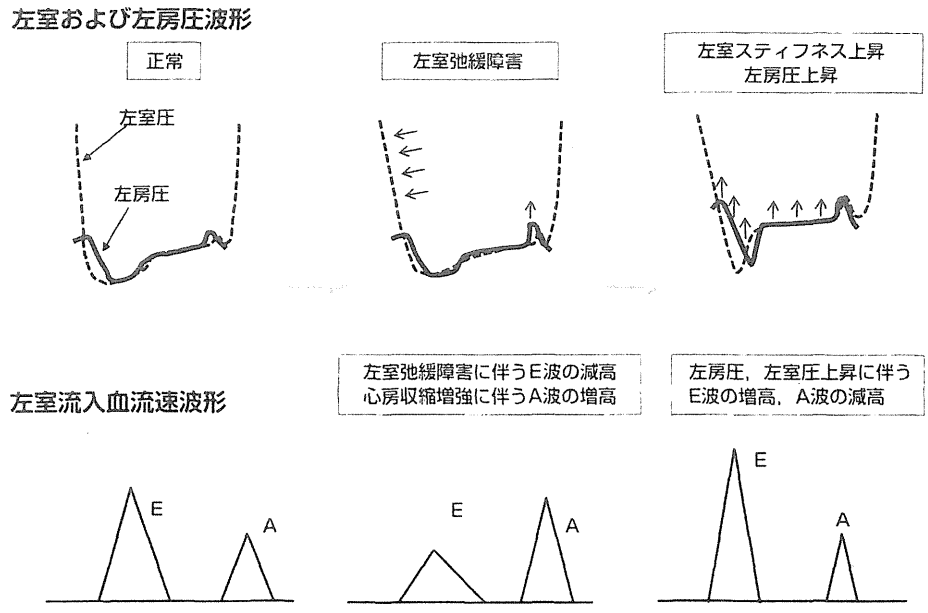
はじめに

人口の高齢化に伴い，心不全患者は年々増加している．世界保健機構(WHO)の統計によると2011年の日本の平均寿命は83歳で，世界一の長寿国である．心不全治療は大きく進歩したが，今でも死亡率は高く，5年生存率は癌と同等との報告がある[1]．また，繰り返す高齢者の心不全増悪による入院は，社会的，医療経済的にも大きな問題となっている．これまで人類が経験したことがない高齢化社会を迎える本邦において，心不全への対策が急務である．

老化に伴う心機能の低下は，日には捉えにくい拡張機能の低下が主体である．高齢者の心不全の特徴の1つに，左室駆出率(Left Ventricular Ejection Fraction：LVEF)の保たれた心不全，拡張不全が多いことが知られており(表1)，心不全患者の約30～50%は拡張不全であることが報告されている[2]．心機能は収縮機能と拡張機能とに分けられるが，心機能の指標に，見た目にわかりやすいLVEFが広く臨床で用いられるため，心機能＝収縮機能と誤解される面があった．しかし，見た目では捉えることが難しい拡張機能障害の重要性が注目されるようになり，LVEFの保たれた心不全の存在とその主たる病態が拡張機能障害であることが広く認識されるようになった．収縮不全は同時に拡張機能の低下を伴うことや，拡張不全もLVEF以外の収縮機能の指標は低下がみられるなど両者の病態はオーバーラップしていることから，最近は収縮不全をEFが低下した心不全，Heart Failure with Reduced EF (HFREF)，拡張不全をEFが保たれた心不全，Heart Failure with Preserved EF (HFPEF)と呼ぶことが一般的となっている．便宜上，本章では従来の拡張不全の呼び方を用いる．加齢と密接に関係するこの拡張不全について最新の知見を述べたい．



Key Words
拡張不全
収縮不全
加齢
左室駆出率



これまでの疫学調査によると拡張不全は，高齢，女性，高血圧の患者に多いことが報告されている．また，肥満，糖尿病，心房細動，慢性腎臓病，睡眠時無呼吸症候群などの合併も多い[2]．わが国の心不全疫学調査，JCARE-CARDによると心不全で入院した患者のうち，LVEF＞50%で弁膜症を除外した心不全を拡張不全と定義した場合，約3割(26%)が拡張不全であった[3]．その特徴は高齢，女性，非虚血性心疾患，高血圧，心房細動，貧血，慢性腎臓病の合併が多く，欧米の報告と同様の特徴を有していた．

また，予後に関しては収縮不全と差はみられず，LVEFが良くても，決して軽症ではないことが明らかとなった．最近の報告では収縮不全と拡張不全では死亡や再入院の原因が違うことが知られている．全死亡でみると収縮不全と拡張不全で差はないが，心血管死は拡張不全で少なく非心血管死が多い[4,5]．また，収縮不全に比べ心不全入院は少なく非心臓疾患による入院が多い[6]．拡張不全は高齢者が多いため合併する非心臓疾患が再入院や予後に影響している可能性を示唆している．したがって，拡張不全に対する対策は非心臓疾患を含めた包括的な管理も重要と考えられる．

加齢に伴う心臓の構造変化としては，心筋肥大や線維化を生じ，心室や心房の機能障害を招く[7]．また血管機能障害や自律神経障害による心拍反応の低下は運動耐容能の低下に関与している．拡張不全では生理的なこれらの加齢変化が病的に進行している[7,8]．

左室から全身に必要とされる血液を送り出す機能を収縮機能とすると，拡張機能はその血液を左房から左室に受け入れる機能と捉えることができる．拡張機能が障害されると血液を受け入れることができなくなり，血液のうっ滞を起こし肺うっ血を来す．

拡張機能は左室弛緩能(心筋の能動的な拡張)と左室スティフネス(心筋の受動的硬さ)とに分けられる．左室収縮に伴う血液の駆出後，左室

弛緩により左室圧が下降して左室圧＜左房圧となると，左房－左室の圧格差により血液の流入が始まる．左室弛緩能が障害されると，左室圧の下降速度が低下するため左室流入障害を招き（左室流入血流波形のE波の減高），心房収縮でそれを代償する（左室流入血流波形のA波の増高）．心房細動では心房収縮が欠如することと，不規則な心拍と頻脈により十分な左室弛緩が得られず，血液の流入障害を招くと考えられる[8]．

一方，左室スティフネスは，いわゆる左室の硬さで，急速流入後期から心房収縮期における左室流入動態に影響を及ぼす．硬い左室では血液流入に伴う左室圧上昇が顕著となり，左房－左室の圧較差が急速に消失するため左室流入障害を招く．それを代償するため，左房から左室への血液の流入を左房圧の上昇（E波の増高）で維持した結果，肺うっ血を来し心不全を発症するものと考えられる（図2）．

拡張不全には高血圧の合併が多く，圧負荷に伴う心筋肥大，心筋の線維化が心不全発症に重要な役割を果たしている．高血圧性拡張不全の動物モデルによる経時的な左室形態および組織学的変化の検討では，まず求心性リモデリングが生じ，これに引き続いて代償性の心筋肥大が生じる．その後さらに過剰な心筋肥大と線維化が生じる．初期の代償性心肥大の形成にはカルシニュリンの関与が示唆されている[9]．

一方，アンジオテンシンⅡやエンドセリンなどは初期の心肥大には関与しておらず，代償性心肥大に引き続いてみられる病的な心筋肥大と線維化に関与している[10]．代償性肥大期に左室弛緩障害が生じ，病的な心筋肥大および線維化の進行とともに心筋スティフネスの増高が生じる．すなわち，弛緩障害にスティフネスの亢進が上乗せされることで拡張不全が発症すると考えられる．

心不全は全身疾患であり，その病態は心機能だけで規定されるものでない．加齢とともに認められる心臓以外の因子の変化が心不全発症に密接に関与している（図3）．

(1)性　差

女性は男性よりも加齢に伴う左室弛緩速度の低下，心筋および血管のステイフネスの増加が顕著である[11]．

(2)高血圧

高血圧は拡張不全の最も重要なリスク因子である．心筋肥大，線維化をもたらし拡張機能の低下に影響する．また，血管の内皮機能障害による血管反応の異常を招き運動耐容能の低下，心不全の発症，増悪に関与している[2]．

(3)自律神経障害

運動中の心拍反応の低下（chronotropic incompetence）により，運動に見合った心拍出量が十分に得られず，運動耐容能の低下に関与している[8]．

(4)慢性腎臓病

腎機能障害による体液貯留は収縮不全だけでなく拡張不全においても心不全の発症，増悪に寄与している．腎血管狭窄は急性の肺水腫の原因となるので，高血圧と腎障害を有する拡張不全の患者では合併に注意が必要である[2]．

(5)貧　血

貧血は心不全患者の予後規定因子として知られているが，収縮不全に比べ拡張不全に合併が多い．末梢組織への酸素運搬能の低下や，末梢血管抵抗の低下に伴う心拍出量の増加による心負荷への関与が推測されている[12]．

(6)低アルブミン血症

高齢者の拡張不全では，低アルブミン血症による浸透圧の低下が肺水腫の増悪に関与しているとの報告がある[13]．また低アルブミン血症の合併は高齢者心不全，拡張不全の予後不良因子である[14,15]．

(7)肥　満

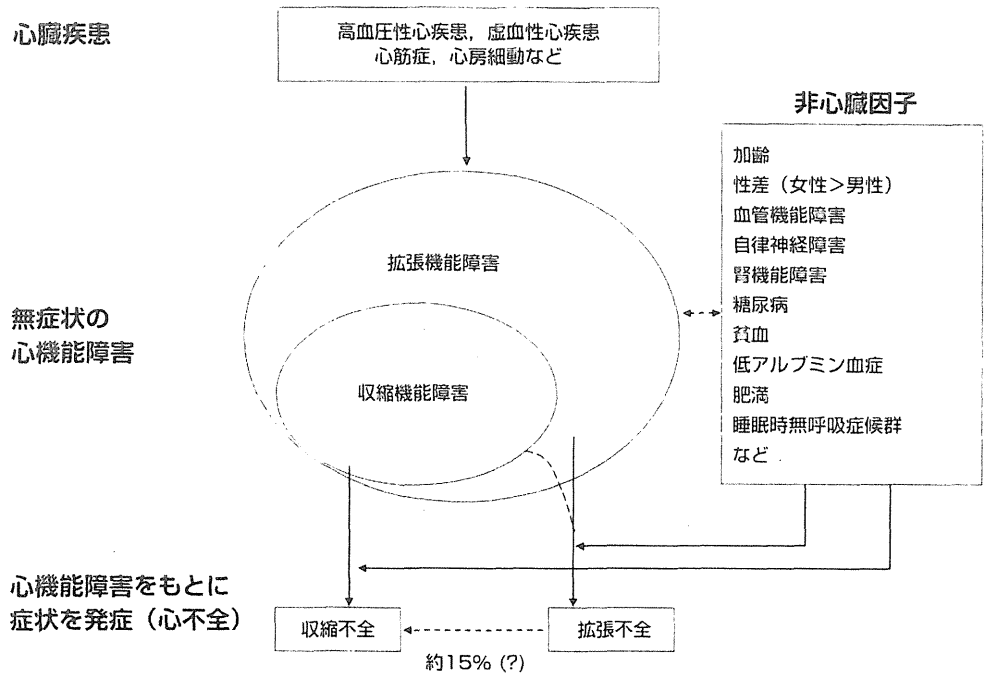
肥満は慢性炎症などが関与し左室拡張機能障害に影響を及ぼす[2]．一方，拡張不全が進行し体重減少を認める症例では収縮不全同様予後が悪い．また逆に肥満が強い症例も予後が悪く，Uカーブ現象が報告されている[16]．

(8)糖尿病

心筋の肥大，線維化に加え，微小血管障害による心筋虚血が拡張機能障害に関与している[2]．

(9)睡眠時無呼吸症候群

肥満，高血圧，糖尿病など拡張不全のリスクとオーバラップしていること，また睡眠時無呼吸症候群に認められる炎症性反応の促進が拡張不全に関与していることが種々のデーターより推測される[17]．



欧州心臓病学会のガイドラインの診断基準として，①心不全による症状があること，②左室収縮機能が保たれていること，③拡張機能の低下がみられることが提唱されている[18]．

まず，症状（息切れ，浮腫など）が心臓由来かを診断することから始まる．ナトリウム利尿ペプチド（BNP，NT-pro BNP）は，呼吸不全を伴う患者の心不全診断に有用なことが報告されており，補助診断に有用である[19]．左室収縮機能保持の基準としてはLVEFが40～50%以上を用いる報告が多い．拡張機能の評価には，左室流入の血流波形（E/A，DT）および組織ドップラー法で記録した僧房弁輪部運動を参考に評価を行う．左室流入波形のE波と僧房弁輪部の拡張早期のE'波の比よりもとめた，E/E'は左房圧と正相関がみられ，間接的に拡張機能の評価に有用である．日本循環器学会の慢性心不全のガイドラインに詳細な診断のフローチャートが記載されているので参照していただきたい[20]．

拡張不全の治療方法はいまだ確立されていない．拡張不全を対象としたCHARM-PRESERVEDでは，アンジオテンシン受容体拮抗薬（ARB），Candesartan投与群で心不全悪化による入院に改善傾向がみられた[21]．一方，Irbesartanを用いたI-PRESERVEDでは，プラセボ群との間に差はみられなかった[22]．高齢者拡張不全を対象としたPEP-CHFでは，アンジオテンシン変換酵素（ACE）阻害薬，Perindopril erbumineは1年間に限れば，心不全増悪による入院を減少させる傾向がみられた[23]．残念ながら，これまでの臨床研究の結果を総合的に評価するとACE阻害薬およびARBなどのレニンアンジオテンシン系阻害薬の有効性は確立されていない．β遮断薬に関しても有効性は確立されていないが，Nevivololを用いたSENIORS試験[24]では，LVEF35%以上の症例でも予後改善効果がみられたことより，拡張不全におけるβ遮断薬の有効性が期待されている．現在，わが国で

β遮断薬 Carvedilol の有効性を検討する J-DHF が行われている[25][26]．また，ミネラルコルチコイド受容体拮抗薬を用いた TOPCAT 試験も現在進行中であり，これらの試験の結果が待たれる[26]．

高齢者が多い拡張不全では QOL の改善(症状の改善や再入院予防)を優先した治療も求められる．ループ利尿薬は速やかに心不全症状を改善することで収縮不全，拡張不全ともに広く用いられているが，本邦で行われた J-MELODIC 試験[27]で長時間作用型のアゾセミドが短時間作用型のフロセミドに比べ心不全の再入院が少ないことが報告されている．そのサブ解析で左室駆出率の違いで予防効果に差がみられなかったことより，拡張不全での有効性が期待される．また，医学的な介入のみならず，患者，家族への教育や，社会的な背景を考慮した包括的な介入も重要である．多職種介入によるチーム医療の重要性が近年注目されており，当院でも医師，看護師，薬剤師，理学療法士，ソーシャルワーカーからなる心不全チームを結成して診療にあたることで心不全の再入院を有意に減少させている．ここで行われている指導内容には，食事療法，運動療法など日常生活においてアンチエイジングとして必要なものが含まれており，拡張不全の包括的なアプローチとして今後期待される[26]．

拡張不全は，人口の高齢化に伴い今後ますます増えていくことが予想される．今なお病態生理や有効な治療方法は確立されていないが，今後のさらなる研究とエビデンスの蓄積により本病態に対する対処法が確立すれば，ひいてはアンチエイジングのヒントとなることが期待される．

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Letter to the Editor

Predictive value of high-molecular weight adiponectin in subjects with a higher risk of the development of metabolic syndrome: From a population based 5-year follow-up data

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Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors on the basis of obesity and insulin resistance. Although the pathophysiology and optimal diagnostic criteria remain controversial, there are evidences that MetS is associated with the prevalence, mortality, and development of cardiovascular disease and type 2 diabetes mellitus [1–3]. Subjects who already have two MetS risk factors at the time of screening test are considered to be likely to develop MetS. Some specific biomarkers may be helpful for selecting subjects at higher risk for the development of MetS from these 'potential MetS patients', and provide clues to prevent development of MetS.

High-molecular weight (HMW)-adiponectin is thought to be the major active form of adiponectin and more useful for predicting insulin resistance [4]. The present study aimed to investigate whether the plasma HMW-adiponectin levels could have an additional diagnostic value to using the conventional MetS risk factors to predict future development of MetS.

This study was originally designed to investigate the efficacy of several biomarkers to predict cardiovascular events in participants in an annual health-check program in Kashima-City, a rural community in Japan. The initial health-check program was carried out from August 2005 to July 2006, and the follow-up survey was conducted after 5 years. Of the 1110 initial study participants, 434 subjects (217 men and 217 women) were eligible for the analysis. All participants provided their written informed consent and the study protocol was conformed to the ethical guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Saga University Faculty of Medicine. MetS was defined based on the National Cholesterol Education Program Adult Treatment Panel III criteria modified by the National Heart, Lung and Blood Institute and the American Heart Association [5]. Blood samples were collected from subjects more than 10 h after the last dietary intake. Plasma HMW-adiponectin levels were measured using a sandwich ELISA kit [6]. All statistical analyses were performed using the SPSS 16.0 Japanese edition for Windows. A P value less than 0.05 was considered to be statistically significant.

A gender-stratified analysis was performed because of the considerable gender differences in plasma HMW-adiponectin levels. Seventy-eight (36.4%) men and 34 (15.9%) women have already had two MetS risk factors at the initial health check program. Among these participants, twenty-six (33.3%) men and 12 (35.3%) women developed MetS during the 5-year follow-up period. In contrast, only 8 (9.4%) men and 5 (6.3%) women with only one MetS risk factor, and 2 (3.7%) men and 0 (0%) women with no MetS risk factor developed MetS, respectively. Therefore we compared between participants with and without development of MetS in the subgroup of the participants with two MetS risk factors at baseline. A multivariate logistic regression model without variable selection to adjust confounding factors showed that plasma HMW-adiponectin level was significantly associated with the development of MetS only in men. By contrast, no significant associations were observed between any variables and development of MetS in women (Table 1). A stepwise multivariate logistic regression model after adjustment for body weight, waist circumference, blood pressure, triglyceride, high-density lipoprotein cholesterol, γ-glutamyl transpeptidase (γ-GTP), and HMW-adiponectin showed that HMW-adiponectin was independently associated with the development of MetS in men (coefficients −0.611, odds ratio 0.543, 95% confidence interval 0.336–0.878, $P=0.013$, data not shown).

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Table 1
Results from a multivariate logistic regression model for predicting the development of MetS in participant with two MetS risk factors.

	Men			Women		
Variables	Coefficients	OR (95%CI)	*P* value	Coefficients	OR (95%CI)	*P* value
Age (years)	−0.042	0.959 (0.874–1.052)	N.S.	−0.266	0.767 (0.509–1.154)	N.S.
Body weight (kg)	−0.083	0.920 (0.818–1.034)	N.S.	0.006	1.006 (0.456–2.220)	N.S.
Waist circumference (cm)	0.126	1.135 (0.955–1.349)	N.S.	0.316	1.371 (0.670–2.809)	N.S.
Systolic BP (mmHg)	−0.001	0.999 (0.936–1.066)	N.S.	−0.050	0.951 (0.723–1.250)	N.S.
Diastolic BP (mmHg)	0.044	1.045 (0.945–1.155)	N.S.	−0.082	0.921 (0.713–1.191)	N.S.
Fasting glucose (mg/dl)	0.010	1.010 (0.947–1.077)	N.S.	−0.619	0.539 (0.131–2.218)	N.S.
TC (mg/dl)	0.010	1.010 (0.947–1.077)	N.S.	0.170	1.185 (0.909–1.545)	N.S.
HDL-C (mg/dl)	0.048	1.049 (0.971–1.133)	N.S.	0.066	1.068 (0.871–1.310)	N.S.
TG (mg/dl)	0.002	1.002 (0.996–1.009)	N.S.	−0.123	0.885 (0.722–1.084)	N.S.
ALT (IU/l)	0.000	1.000 (0.961–1.041)	N.S.	−0.983	0.374 (0.057–2.475)	N.S.
γ-GTP (IU/l)	−0.020	0.980 (0.959–1.002)	N.S.	0.746	2.109 (0.686–6.489)	N.S.
UA (mg/dl)	−0.139	0.870 (0.452–1.675)	N.S.	0.701	2.016 (0.025–162.364)	N.S.
Current smoking (n)	−0.209	0.811 (0.177–3.726)	N.S.	NA	NA	NA
HMW-adiponectin (μg/ml)	−0.896	0.408 (0.224–0.743)	0.003	−1.547	0.213 (0.013–3.577)	N.S.
NT-proBNP (pg/ml)	−0.005	0.995 (0.965–1.025)	N.S.	0.053	1.055 (0.949–1.172)	N.S.
hsCRP (mg/l)	0.006	1.006 (0.602–1.681)	N.S.	−0.793	0.452 (0.105–1.947)	N.S.

BP = blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglyceride; ALT = alanine aminotransferase; γ-GTP = γ-glutamyl transpeptidase; UA = uric acid; HMW-adiponectin = high molecular weight adiponectin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; hs-CRP = high sensitivity C-reactive protein; OR = odds ratio; and CI = confidence interval.

The study participants were separated into 3 groups in ascending order of the plasma HMW-adiponectin levels prior to the analysis. More subjects developed MetS during the 5-year follow-up period in proportion to the decreased plasma HMW-adiponectin levels in men with two MetS risk factors. However, this low was not applicable to men who have one or less MetS risk factor (Fig. 1a). On the other hand, plasma HMW-adiponectin levels were not useful for predicting future development of MetS in women in any stratum of the number of MetS component (Fig. 1b).

The present study demonstrated that the low plasma HMW-adiponectin level was independently associated with the development of MetS in men with two MetS risk factors. Seino et al. have already reported that HMW-adiponectin levels predicted the progression to MetS in a 6-year follow-up study of Japanese men [7]. The present study confirmed their findings, and, additionally, provided information that plasma HMW-adiponectin levels were of little use in predicting the risk of development of MetS in women. Sattar et al. reported that HMW-adiponectin is not associated with the incidence of coronary heart disease in older women [8], and Himbergen et al. recently reported that elevated plasma adiponectin levels are an independent risk factor for the development of all-cause dementia and Alzheimer disease in women [9]. The authors found a threshold effect above which the adiponectin level becomes a risk factor. Previous population-based studies and the current study found that women have significantly higher plasma HMW-adiponectin levels than that of men [10]. It is conceivable that the plasma HMW-adiponectin levels are compensatory increased in some women with the development of MetS; however, it seems to be difficult to distinguish between these subjects.

This study has potential limitations. The prevalence of MetS was 2.5% in women in the present study cohort at baseline. Also relatively small number of subjects developed MetS during the 5-year follow-up period in women. Therefore, the interpretation of the statistical measures, especially in women, could be associated with a potential bias.

In conclusion, a decreased concentration of plasma HMW-adiponectin was independently associated with the development of MetS only in men with two MetS risk factors. It is worth investigating the gender differences in the mechanism of the development of MetS, and the role of HMW-adiponectin.

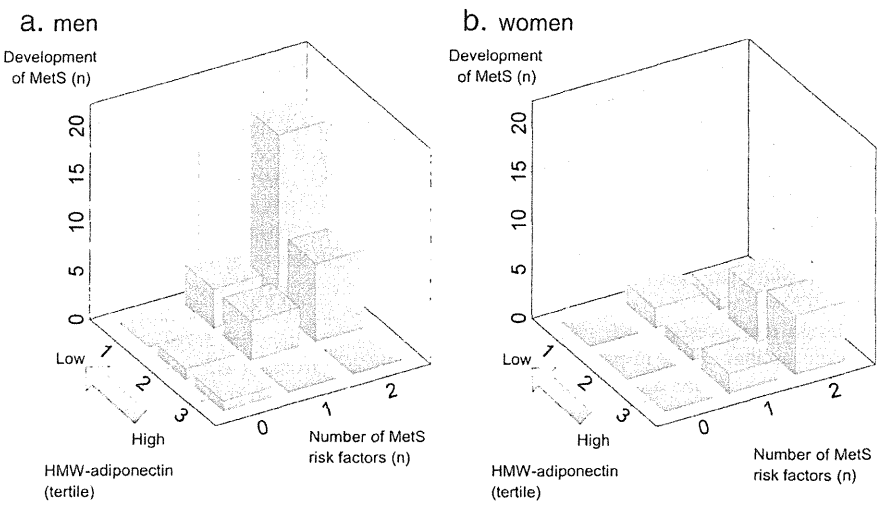

Fig. 1. The incidence of the development of MetS in relation to HMW-adiponectin tertile and number of MetS components. More subjects developed MetS in proportion to the decreased plasma HMW-adiponectin levels in men with two MetS risk factors. However, this low was not applicable to men with one or less MetS risk factor (a). On the other hand, HMW-adiponectin levels were not useful for predicting the development of MetS in women in any stratum of the number of MetS risk factor (b).

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ORIGINAL ARTICLE
Heart Failure

Mode of Death in Patients With Heart Failure and Reduced vs. Preserved Ejection Fraction

– Report From the Registry of Hospitalized Heart Failure Patients –

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Background: The mode of death has not been investigated in the registry data of patients with heart failure and reduced ejection fraction (HFREF) vs. preserved ejection fraction (HFPEF). The aim of the present study was therefore to carry out this comparison.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments in a broad sample of 2,675 patients hospitalized with worsening HF, and followed them for an average of 2.1 years. This study included 323 patients in whom information on both the mode of death and left ventricular EF on echocardiography could be obtained. The mode of death was cardiovascular (CV) in 63% (including 17% sudden, 36% HF, 3% myocardial infarction, and 3% stroke), non-CV in 23%, and unknown in 14%. The prevalence of CV death including sudden death was high in patients with HFREF compared to HFPEF (68% vs. 58%, P=0.020). HF death, the most common mode of death, was similar between groups (37% vs. 35%, P=0.694). In contrast, non-CV mortality was significantly higher in HFPEF than those with HFREF (28% vs. 18%, P=0.021).

Conclusions: In 60–70% of deaths the mode was CV, and HF death was the most common mode of death in either HFREF or HFPEF. The prevalence of sudden death was lower, and that of non-CV death higher, in HFPEF compared with HFREF. (*Circ J* 2012; **76:** 1662–1669)

Key Words: Cardiovascular death; Ejection fraction; Heart failure; Outcome; Sudden death

Approximately half of all patients with chronic heart failure (HF) have been reported to have a normal or nearly normal, preserved, left ventricular ejection fraction (LVEF).[1–4] The clinical characteristics and outcomes in patients with HF and a preserved EF (HFPEF) differ significantly from those with HF and a reduced EF (HFREF).[1–7] Previous studies have demonstrated that patients with HFPEF had a similar mortality risk and equally high rates of rehospitalization as those with HFREF.[3,5–9] In contrast, other studies found that the mortality rate was significantly lower in patients with HFPEF than HFREF.[1,2,4,10] One possible explanation for these discrepancies might be the differences in the mode of death between HFREF and HFPEF, making 1 group more or less vulnerable to specific mode. There have been several limitations in previous studies, however, in which the mode or cause of death was assessed.[11–18] First, they characterized the mode or cause of death in patients with HFREF and little is known about this critical issue in patients with HFPEF. Second, most previous studies merely distinguished between cardiovascular (CV) and non-CV death and no detailed analysis of the mode of death has been performed. Finally, 2 studies with detailed information on these modes were conducted, using a community-based cohort of HF patients from Olmsted Country,[17] and a subgroup of patients enrolled in a randomized clinical trial (RCT), the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve).[18] Therefore, selection bias and influence of therapy could not be completely excluded. To improve the understanding of the pathophysiology and to establish effective management strategies in HFPEF, it is of critical importance to identify the mode of death in these patients and compare it with that in HFREF. In particular, such an analysis needs to be performed in HF patients encountered in routine clinical practice.

The Japanese Cardiac Registry of Heart Failure in Cardiol-

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ogy (JCARE-CARD) studied prospectively the characteristics and treatments in a broad sample of 2,675 patients hospitalized with HF, and followed up the outcomes including death and rehospitalization due to worsening HF for an average of 2.1 years.[7,19–22] The aim of the present study was to examine the mode of death in HF patients registered in JCARE-CARD and compare the distribution of the specific mode of death in patients with HFPEF vs. HFREF.

Methods

Patients

The details of the JCARE-CARD have been described previously.[7,19,21–25] Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. For each patient, baseline data included (1) age, sex, and body mass index (BMI); (2) causes of HF; (3) medical history; (4) prior procedures; (5) vital signs; (6) laboratory data; (7) echocardiographic data; and (8) medication use at discharge. The data were registered using a Web-based electronic data capture system licensed by JCARE-CARD (www.jcare-card.jp).

A total cohort of 2,675 patients was registered in JCARE-CARD at the time of the index hospitalization. A total of 126 patients (4.7%) died during the index hospitalization and 244 patients (9.1%) were missed during the follow-up. Follow-up data could thus be obtained in 2,305 out of 2,675 patients (86.2%), and 474 patients (20.6%) died during follow-up. Out of 2,305 patients, information on LVEF was obtained on echocardiography at the time of index hospitalization in 2,020 patients, and 393 patients (19.5%) died during the follow-up. Information on both mode of death and LVEF could be obtained in 323 patients (68% of all deaths).

Definitions of Mode of Death

The mode of death was assigned by the cardiologists in the participating hospitals based on the information including case records, discharge summary, and autopsy reports, and information on all the deaths and mode of death were reviewed by the steering committee. According to the previous study, mode of death categories were defined as follows: (1) sudden death; (2) HF death; (3) myocardial infarction (MI) death; (4) cerebrovascular accident death; (5) CV procedure death; (6) other cardiac death; (7) other vascular death; (8) non-CV death; and (9) unknown death.[18]

Sudden death was defined as an unexpected death in a previously clinically stable patient. Patients in this category had recent human contact before the event. This category includes patients who after attempted resuscitation became comatose and then died. For patients who died and who had been out of contact for prolonged (generally >1 week) or unknown periods of time, the death was classified as unknown. When sufficient information was available, sudden death was subcategorized as with or without preceding CV symptoms. In the absence of such information, the sudden death event was subcategorized as unknown.

HF death was defined as a death that occurred as a result of worsening or intractable HF. Terminal arrhythmias associated with HF deaths were classified as a HF death. HF secondary to a recent MI was classified as an MI death. Patients with worsening HF had many of the following features: symptoms of HF, signs on physical examination of HF, and diagnostic evidence of HF such as an abnormal chest X-ray, significant increase in B-type natriuretic peptide or N-terminal prohormone B-type natriuretic peptide, or prerenal azotemia. When sufficient information was available, HF death was subcategorized as with or without low output and/or congestion. In the absence of such information, the HF death event was subcategorized as unknown. Low output was indicated by symptoms (confusion, weakness, and cold periphery) and signs (poor peripheral perfusion, systolic blood pressure <90 mmHg, and anuria or oliguria).[26] Congestion was indicated by symptoms and signs on physical examination, chest X-ray, and non-invasive and invasive measurements.

MI death was defined as a death that occurred after a verified definite acute MI. In cases of death occurring outside the hospital, a death was classified as an MI death if the autopsy findings showed a recent MI or a recent coronary thrombus. The criteria necessary to satisfy the diagnosis for an acute, evolving, or recent acute MI included the following: positive changes or exceeding the upper limits of normal in biochemical markers of myocardial necrosis (troponin or creatine kinase-MB) and ischemic cardiac symptoms, electrocardiogram changes indicating the new onset ischemia or development of abnormal Q wave, and/or evidence of myocardial necrosis or a new appearance of wall motion abnormalities on the imaging tests.[27] Cerebrovascular accident death was defined as a death that occurred after a hospital-verified definite stroke. In cases of death occurring outside the hospital, a death was classified as a cerebrovascular accident death if autopsy findings showed a recent stroke. Stroke was defined as a persistent disturbance (≥24 h) of focal neurological function resulting in symptoms thought to be due to atherothrombotic or thrombotic cerebral infarction, embolus, or evidence of hemorrhage or for which there was no certain cause. Diagnosis required characteristic history, physical examination, imaging techniques, and/or autopsy data. CV procedure death was defined as a death that occurred during the operative or perioperative period that could be directly attributed to the procedure itself. Other cardiac death was defined as a death that could be attributed to a cardiac reason but was not 1 of the other modes listed here. For example, deaths resulting from valvular heart disease were considered other cardiac deaths. Other vascular death was defined as a death that could be attributed to a vascular reason. These included such events as pulmonary embolism, aortic dissection, or aortic rupture.

Non-CV death was defined as a death that could be attributed to a non-CV cause. These included subcategories such as renal, respiratory, cancer, trauma, infection/sepsis, suicide, and other. Unknown death was defined as a death in which no specific morbid event classification could be assigned.

Statistical Analysis

Patient characteristics and treatments were compared using Pearson chi-squared test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. Cumulative event-free rates and incidence of outcomes during the follow-up were derived using the method of Kaplan and Meier. The relationship between predictors and outcomes was evaluated using multivariate adjustment. The covariates age, sex, BMI, diabetes mellitus, New York Heart Association (NYHA) functional class, estimated glomerular filtration rate (eGFR), hemoglobin, and LVEF, were used to develop the post-discharge Cox proportional hazard models.

The results are reported as hazard ratio, 95% confidence interval, and P-value. $P<0.05$ was used as a criterion for variables to stay in the model. SPSS version 16.0J for Windows was used for all statistical analysis.

Table 1. Patient Characteristics vs. LVEF

Characteristics	Total (n=323)	HFREF (n=154)	HFPEF (n=169)	P-value
Age (years)	75.5±12.6	73.4±12.6	77.5±12.2	0.001
Male (%)	62.5	70.8	55.0	0.003
BMI (kg/m²)	21.2±3.4	21.2±3.3	21.2±3.5	0.557
Causes of heart failure (%)				
Ischemic	37.5	46.8	29.0	0.001
Valvular	29.1	18.2	39.1	<0.001
Hypertensive	20.1	11.0	28.4	<0.001
Cardiomyopathy	17.3	25.3	10.1	<0.001
Medical history (%)				
Hypertension	47.8	36.6	58.0	<0.001
Diabetes mellitus	29.8	34.4	25.6	0.084
Dyslipidemia	21.8	25.5	18.5	0.127
Prior stroke	18.1	15.4	20.5	0.245
COPD	7.3	7.9	6.7	0.684
Smoking	37.2	41.0	33.8	0.196
Prior MI	32.8	45.7	20.9	<0.001
Atrial fibrillation	36.2	28.6	43.4	0.006
Sustained VT/VF	11.7	14.6	8.9	0.123
Procedures (%)				
PCI	19.9	27.6	12.8	0.001
CABG	11.0	15.8	6.6	0.009
Valvular surgery	4.4	3.3	5.4	0.354
PPM	1.9	3.2	0.6	0.078
ICD	3.2	5.4	1.2	0.036
CRT	2.9	4.8	1.2	0.064
Vital signs at discharge				
NYHA functional class 1/2 (%)	87.2	81.0	92.8	0.002
Heart rate (beats/min)	70.6±12.3	72.5±13.5	68.9±10.9	0.017
SBP (mmHg)	115.4±19.1	110.9±17.9	119.4±19.3	<0.001
DBP (mmHg)	64.0±11.1	62.3±11.0	65.5±11.0	0.008
Laboratory data at discharge				
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	42.4±24.8	42.6±24.7	42.3±25.0	0.820
Serum uric acid (mg/dl)	7.9±2.5	8.1±2.5	7.7±2.4	0.306
Hemoglobin (g/dl)	11.1±2.4	11.5±2.5	10.8±2.3	0.055
Plasma BNP (pg/ml)	579±695	637±774	523±608	0.166
Echocardiographic data				
LV EDD (mm)	56.0±11.5	61.6±10.6	51.0±9.8	<0.001
LV ESD (mm)	43.8±13.2	53.0±10.3	35.5±9.6	<0.001
IVST (mm)	10.4±2.9	9.6±3.1	11.0±2.5	<0.001
LV PWT (mm)	10.7±2.7	10.2±2.8	11.2±2.6	<0.001
LVEF (%)	43.0±18.1	27.0±7.6	57.5±11.3	<0.001
Medications at discharge (%)				
ACE inhibitor	38.4	44.9	32.5	0.025
ARB	36.5	40.8	32.5	0.129
ACE inhibitor or ARB	69.4	76.2	63.2	0.013
β-blocker	41.9	51.7	33.1	0.001
Diuretics	90.3	89.8	90.8	0.766
Loop diuretics	84.5	83.7	85.3	0.697
Spironolactone	38.1	39.5	36.8	0.632
Digitalis	34.5	38.1	31.3	0.208
Ca channel blocker	23.2	13.6	31.9	<0.001
Nitrates	23.9	26.5	21.5	0.297
Anti-arrhythmics	21.6	31.3	12.9	<0.001
Aspirin	51.9	53.7	50.3	0.546
Warfarin	36.1	40.8	31.9	0.103
Statin	17.4	19.7	15.3	0.309

(Table 1 continued the next page.)

Data given as % or as mean±SD.
LV, left ventricular; EF, ejection fraction; HFREF, heart failure with reduced EF; HFPEF, heart failure with preserved EF; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; EDD, end-diastolic diameter; ESD, end-systolic diameter; IVST, interventricular septal thickness; PWT, posterior wall thickness; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

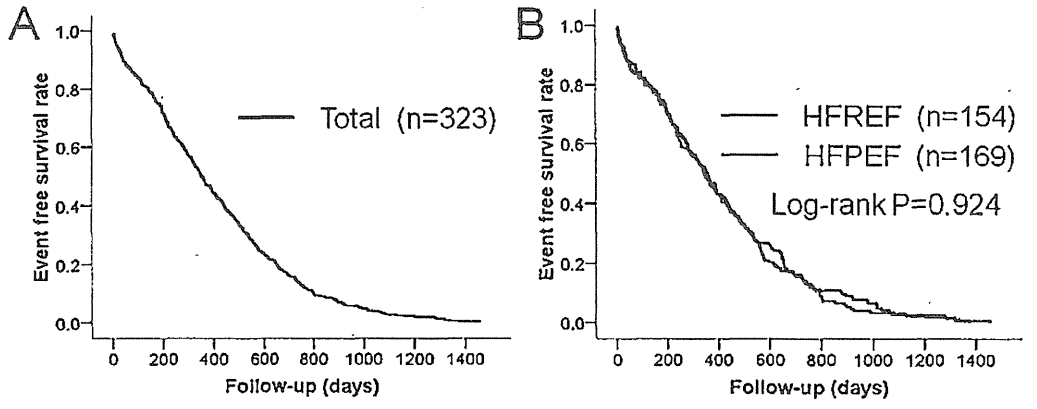

Figure 1. Kaplan-Meier curves for survival rate in (A) total patients (n=323) and (B) heart failure and reduced ejection fraction (HFREF; red line, n=154) vs. HF and preserved EF (HFPEF; black line, n=169).

Table 2. Mode of Death vs. LVEF

Mode of death	Total (n=323)	HFREF (n=154)	HFPEF (n=169)	P-value
Sudden death, n (% of total death)	54 (17)	36 (23)	18 (11)	0.002
With preceding CV symptoms, n (% of sudden death)	30 (56)	21 (58)	9 (50)	
Without preceding CV symptoms, n (% of sudden death)	4 (7)	3 (8)	1 (6)	0.714
Unknown, n (% of sudden death)	20 (37)	12 (33)	8 (44)	
HF death, n (% of total death)	116 (36)	57 (37)	59 (35)	0.694
Low output, n (% of HF death)	15 (13)	6 (11)	9 (15)	
Congestion, n (% of HF death)	16 (14)	2 (4)	14 (24)	0.006
Low output+congestion, n (% of HF death)	74 (64)	44 (77)	30 (51)	
Unknown, n (% of HF death)	11 (9)	5 (9)	6 (10)	
MI death, n (% of total death)	11 (3)	3 (2)	8 (5)	0.168
Cerebrovascular accident death, n (% of total death)	11 (3)	4 (3)	7 (4)	0.445
CV procedure death, n (% of total death)	1 (0)	1 (1)	0 (0)	0.294
Other cardiac death, n (% of total death)	4 (1)	2 (1)	2 (1)	0.925
Other vascular death, n (% of total death)	6 (2)	2 (1)	4 (2)	0.478
Non-CV death, n (% of total death)	75 (23)	27 (18)	48 (28)	0.021
Renal, n (% of non-CV death)	11 (15)	4 (15)	7 (15)	
Respiratory, n (% of non-CV death)	9 (12)	2 (7)	7 (15)	
Cancer, n (% of non-CV death)	28 (37)	12 (44)	16 (33)	
Trauma, n (% of non-CV death)	0 (0)	0 (0)	0 (0)	0.778
Infection/sepsis, n (% of non-CV death)	20 (27)	6 (22)	14 (29)	
Suicide, n (% of non-CV death)	0 (0)	0 (0)	0 (0)	
Other, n (% of non-CV death)	7 (9)	3 (11)	4 (8)	
Unknown death, n (% of total death)	45 (14)	22 (14)	23 (14)	0.861

CV, cardiovascular. Other abbreviations as in Table 1.

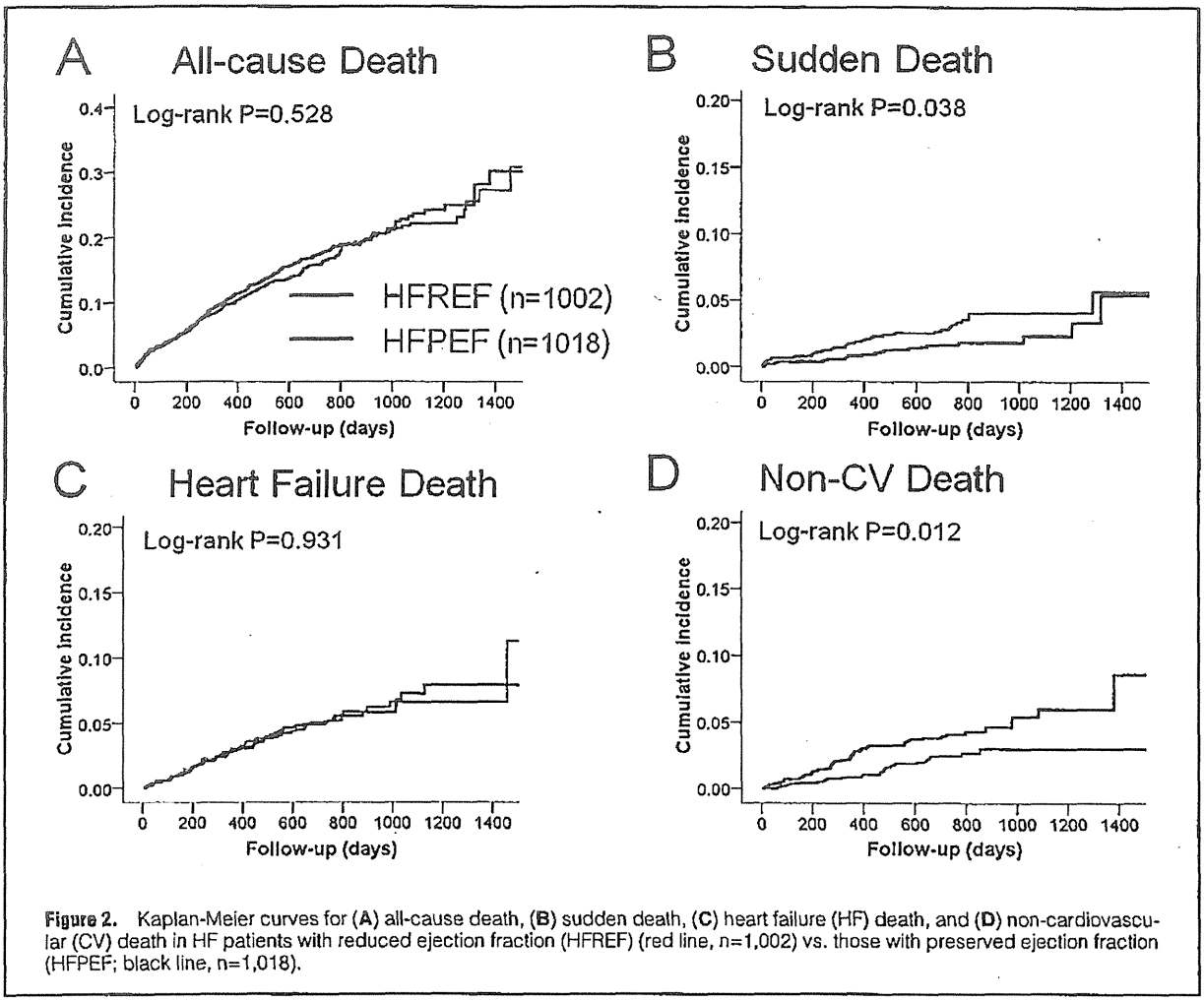

Figure 2. Kaplan-Meier curves for (**A**) all-cause death, (**B**) sudden death, (**C**) heart failure (HF) death, and (**D**) non-cardiovascular (CV) death in HF patients with reduced ejection fraction (HFREF) (red line, n=1,002) vs. those with preserved ejection fraction (HFPEF; black line, n=1,018).

Results

Patient Characteristics

Among a total cohort of 323 patients, the mean age was 75.5±12.6 years, 62.5% were men, 37.5% had ischemic heart disease for HF etiology, and 87.2% had mild HF symptoms at discharge (NYHA functional class I or II). The mean LVEF on echocardiography was 43% (**Table 1**).

Patients were divided into 2 groups according to LVEF: <40% (HFREF group; n=154, 48%) or ≥40% (HFPEF group; n=169. 52%; **Table 1**). Patients with HFPEF were significantly older and more frequently female. The prevalence of valvular and hypertensive etiology was higher, and that of ischemic heart disease and cardiomyopathy lower, compared to HFREF. The HFPEF patients had a higher prevalence of comorbidities including hypertension and atrial fibrillation, whereas prior MI was more common in patients with HFREF. The HFPEF patients underwent fewer percutaneous coronary interventions and coronary artery bypass grafts, and had fewer implantable cardioverter defibrillators. Patients with HFPEF had milder symptoms according to NYHA functional class at discharge. Systolic blood pressure and diastolic blood pressure at discharge were significantly higher in patients with HFPEF. As expected, echocardiography showed that LVEF was higher, and LV end-diastolic and end-systolic diameters were smaller in patients with HFPEF. LV wall thickness was greater in these patients.

The use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, and anti-arrhythmic drugs at hospital discharge was significantly lower in patients with HFPEF. Conversely, Ca channel blocker was more commonly prescribed for them.

All-Cause Death and Mode of Death

There was no significant difference in Kaplan-Meier curves for survival rates between patients with HFPEF and HFREF (P=0.924; **Figure 1**). **Table 2** lists the mode of death measured as number of patients and percentage of total mortality or categories. Out of total 323 deaths, 203 deaths (63%) were CV, 75 (23%) were non-CV, and 45 (14%) were unknown. HF death was the most common mode of death and HF death with low output plus congestion was the most common subcategory.

Among CV death, distribution of subcategories differed between HFREF and HFPEF. Sudden death was less frequent in patients with HFPEF than HFREF (11% vs. 23%, P=0.002). The distribution of subcategories of sudden death was similar between HFPEF and HFREF (P=0.714).

Table 3. Predictors of Sudden Death and HF Death

	Predictors	Adjusted HR	95%CI	P-value
Sudden death				
HFREF	Hemoglobin (per 1-g/dl decrease)	1.234	1.011–1.505	0.038
HFPEF	eGFR (per 1-ml·min^{-1}·1.73m^{-2} decrease)	1.026	1.001–1.051	0.040
HF death				
HFREF	eGFR (per 1-ml·min^{-1}·1.73m^{-2} decrease)	1.035	1.013–1.057	0.002
	Age (per 1-year increase)	1.046	1.003–1.091	0.035
	NYHA functional class (per 1-class increase)	2.437	1.214–4.892	0.012
HFPEF	Age (per 1-year increase)	1.033	1.002–1.065	0.038
	Hemoglobin (per 1-g/dl decrease)	1.165	1.009–1.346	0.037

The Cox regression model was used in the analysis adjusted for the following covariates; age, sex, BMI, diabetes mellitus, NYHA functional class, eGFR, hemoglobin, and LVEF.
HF, heart failure; HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

HF death was the most common mode of death in patients with HFPEF as well as HFREF (35% vs. 37%, P=0.694). For HF death, there were more deaths in HFREF patients due to low output plus congestion than in the HFPEF patients (P=0.006). The mode of death distribution was similar even when the patients were divided into 2 groups according different definition; to LVEF <40% or ≥50% (data not shown).

Figure 2 shows Kaplan-Meier curves for the cumulative incidence of all-cause death, sudden death, HF death, and non-CV death in patients with HFREF and HFPEF during follow-up. Again, the incidence of sudden death was higher in HFREF than in HFPEF (P=0.038), and that of non-CV death was higher in HFPEF than in HFREF (P=0.012), while those of all-cause death and HF death were similar between the groups.

The independent predictor for sudden death was lower hemoglobin in patients with HFREF and lower eGFR in patients with HFPEF (**Table 3**). HF death was independently associated with lower eGFR, higher age, and higher NYHA functional class in patients with HFREF and with higher age and lower hemoglobin in patients with HFPEF (**Table 3**).

Other CV death including MI, cerebrovascular accident, and others was similar between groups. Non-CV death was significantly higher in patients with HFPEF than HFREF (28% vs. 18%, P=0.021). Distribution of subcategories of non-CV death was similar between groups (P=0.778). Unknown death was similar between HFREF and HFPEF (14% vs. 14%, P=0.861; **Table 2**).

Discussion

Using the registry data of hospitalized HF patients, the present study has made the following findings. First, 63% of the deaths among HF patients during the follow-up were CV, 23% non-CV, and 14% unknown. Second, HF death was the most common mode of death in patients with HFPEF as well as HFREF. Third, the distribution of the mode of death categories in patients with HFPEF differs from that in patients with HFREF. There were fewer sudden deaths and more non-CV deaths in HFPEF patients than in HFREF patients.

In our previous study using the same registry data, patients with HFPEF had a similar mortality risk and equally high rate of rehospitalization as those with HFREF.[7] The rate of in-hospital death (6.5% vs. 3.9%, P=0.030) and death during long-term follow-up after discharge (22.7% vs. 17.8%, P=0.058) were slightly higher in patients with HFPEF, which, however, did not differ after multivariate adjustment. Patients with HFPEF had a similar rate of rehospitalization due to worsening HF compared with patients with HFREF (36.2% vs. 33.4%, P=0.515).[7]

The present study shows that there are differences in the distribution of the mode of death categories between HFREF and HFPEF (**Table 2**). The most common mode of death was HF death in both HFREF and HFPEF patients (37% vs. 35%, P=0.694). This might be due to the fact that the present study included patients hospitalized due to worsening HF. HF death was subcategorized as with or without low output and/or congestion in the present study. Combined low output and congestion was the most common subcategory in HFREF. In contrast, patients with HFPEF had congestion more frequently than in HFREF. Sudden death was higher in HFREF than in HFPEF (23% vs. 11%, P=0.002). Non-CV death was lower in HFREF than in HFPEF (18% vs. 28%, P=0.021), consistent with the previous study based on results from the I-Preserve trial (15% vs. 30%)[18] and a community-based cohort study of HF patients from Olmsted Country (36% vs. 49%).[17] These findings indicate that patients with HFPEF carry a lower risk of sudden death, but not overall and HF death. This might be due to higher age and extensive comorbidities in HFPEF patients (**Table 1**). This underscores the importance of the identification and management of comorbidities among patients with HF, especially with HFPEF. Moreover, this also highlights the difficulties in the development of effective treatment strategies in patients with HFPEF because non-cardiac comorbid conditions may interfere with HF treatment and adversely affect outcomes.[28]

The present study demonstrated that, in patients with HFPEF, the mode of death was non-CV in 28% and CV in 63% (including 11% sudden, 35% HF, 5% MI, and 4% stroke). In the I-Preserve trial, it was non-CV in 30% and CV in 60% (including 26% sudden, 14% HF, 5% MI, and 9% stroke).[18] Therefore, the prevalence of sudden death was lower (11% vs. 26%), whereas that of HF death was higher (35% vs. 14%) in the present study than in the I-Preserve trial. The rate of HF death was reported to be 21% in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved, and 28% in the Digitalis Investigator Group (DIG)-Preserved.[13,15] Therefore, the rate of HF death in the present study was higher than in the previous studies. These differences may relate in part to the differences in LVEF cut-offs, the severity of HF, and the type of patients studied (outpatients vs. hospitalized patients). Moreover, the differences between the present registry and the clinical trial data illustrate the limitations of extrapolating the findings obtained from RCT into the real world. Even though the recent study from the I-

Preserve trial provided a detailed analysis regarding the mode of death, it included only patients with HFPEF and could not compare patients with HFPEF vs. those with HFREF.[18] In contrast, the present study analyzed HF patients independently of LVEF and could compare the mode of death in both HFREF and HFPEF patients enrolled within the registry. Regardless of the type of patients studied, HF death and sudden death were the most common CV death not only in HFREF but also in HFPEF. These results clearly demonstrate that effective treatment strategies against HF and sudden death are also critically needed in patients with HFPEF.

Study Limitations

Several limitations inherent in the design of the registry should be considered. First, this study included only patients who could be followed and whose data for both mode of death and LVEF were obtained. Thus 68% of all deaths could be included in the analysis, leading to a substantial selection bias. But this underscores the importance and relevance of the present findings to routine clinical practice. Second, the data were dependent on the accuracy of documentation and abstraction by the individual medical centers that participated in the study. Even though we could not completely exclude the possibility that some deaths could be misclassified, it would occur in both the HFPEF and the HFREF patients, therefore it should not affect the primary findings of the present study. Moreover, it is sometimes difficult to identify the mode of death only by clinical findings, even when complete information was obtained. Therefore, unknown death was defined as a death in which no specific morbid event classification could be assigned. Further, misclassification should not be a major problem because the present study used detailed and well-defined categories of mode of death.

Conclusions

In the patients hospitalized with worsening HF, the mode of 60–70% of death was CV, and HF death was the most common mode of death in either HFREF or HFPEF. In HFPEF the prevalence of sudden death was lower, and that of non-CV death higher, compared with HFREF. More widespread use of the standard medication for HF might reduce the risk of death also in patients with HFPEF. Effective management strategies are critically needed for HFPEF.

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