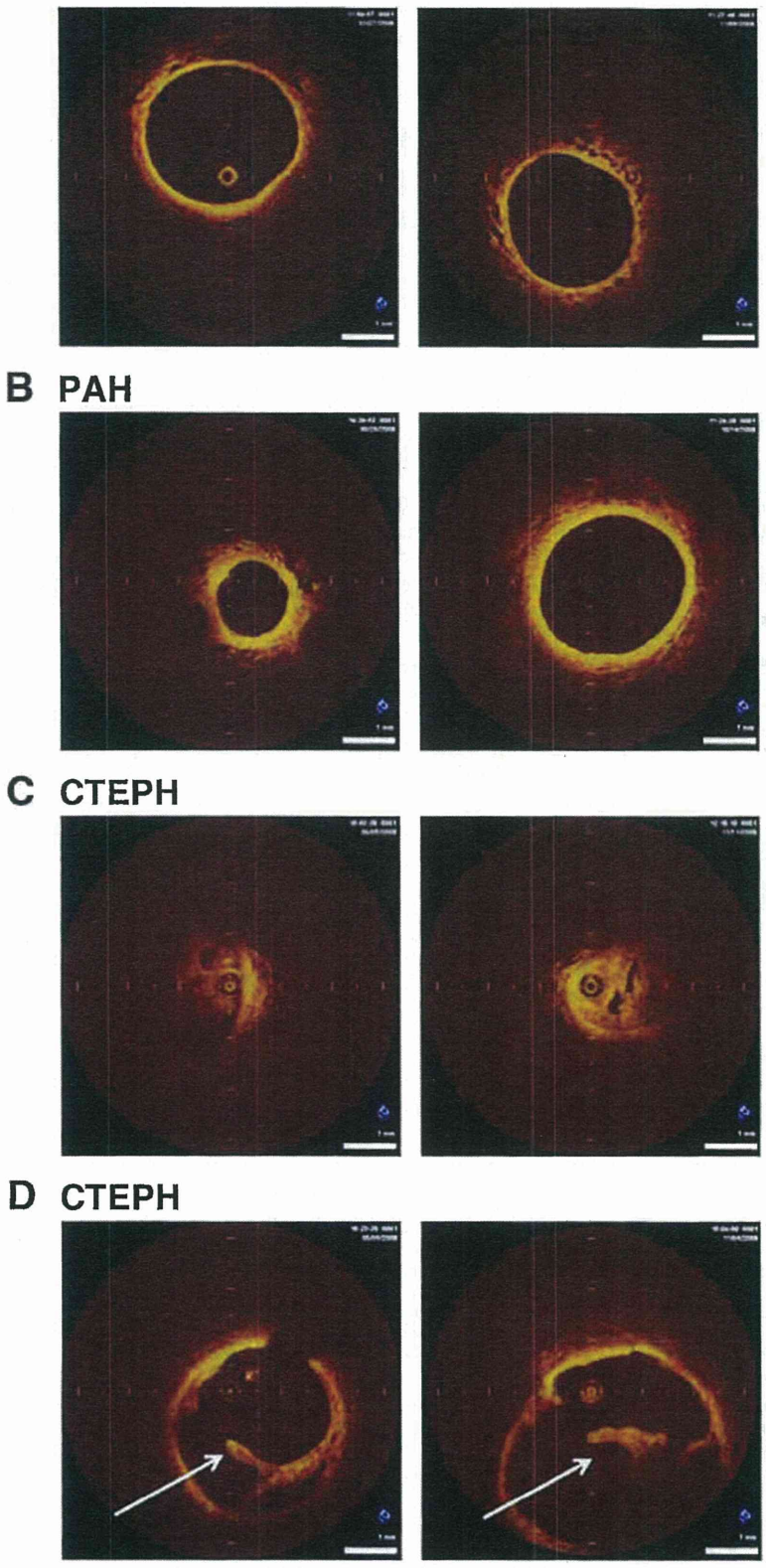

Figure. Optical coherence tomography (OCT) of the pulmonary arteries from (**A**) control subjects, (**B**) pulmonary artery hypertension (PAH) patients, and (**C**, **D**) chronic thromboembolic pulmonary hypertension (CTEPH) patients. The media of the pulmonary artery is thickened in (**B**) PAH, as compared with (**A**) controls. In contrast, in CTEPH, the pulmonary arteries have a very different OCT appearance with either (**C**) thrombotic occlusion and/or (**D**) luminal flaps (arrows). Bar, 1.0 mm.

admitted to Tohoku University Hospital from February 2009 to December 2009 and underwent right heart catheterization including OCT (**Table**). Pulmonary arteries >1 mm in diameter had no obstruction in the control or PAH subjects, although the media of the arteries appeared to be thickened in PAH subjects compared with controls (**Figures A,B**). In contrast, in all cases of CTEPH, we obtained completely different findings as compared with the control or PAH subjects; half of the CTEPH patients had occlusion of the pulmonary arteries, probably by thrombus (**Figure C**), and more than half of them had flaps in the lumen of the pulmonary arteries (**Figure D**; **Table**).

Pathohistological studies have demonstrated that idiopathic PAH is associated with abnormal vascular structures, including medial and/or intimal hypertrophy, concentric and/or eccentric intimal fibrosis, obstruction in the arterial lumen, and aneurysmal dilatation in vessels <300 mm in diameter.[5–7] In contrast, CTEPH is caused by the obstruction of pulmonary arteries by thrombus and is mainly observed in large vessels.[8,9] The present results indicate that OCT is a potentially useful tool for the differential diagnosis of distal type CTEPH from PAH.

Acknowledgment

The present work was supported in part by grants-in-aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

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特集　心不全パンデミックにどう対処するか

疫学：慢性心不全患者は爆発的に増加している*

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Key Words : heart failure, super-graying society

はじめに

慢性心不全は心筋障害により心臓のポンプ機能が低下し，末梢主要臓器の酸素需要量に見合うだけの血液量を絶対的または相対的に拍出できない状態であり，肺，体静脈系または両系にうっ血をきたし日常生活に障害を生じた病態である[1]．日本人の虚血性心疾患有病者数の増加，超高齢化社会に伴う心不全の増加，標準的治療の浸透や植え込み型除細動器(ICD)や心臓再同期療法(CRT)などのデバイス治療による心不全治療の改善に伴う心不全治療後の生存者数増加によって，慢性心不全患者は爆発的に増加することが予想される．日本人を対象とした慢性心不全の疫学研究では，2030年には日本の総人口は1億1千万人に減少するのに対して心不全患者は130万人に達すると推定されており[2]，これは2030年には日本人の約100人に1人が心不全患者となることを意味する．患者数増加に従って近い将来，心不全患者はもはや循環器内科外来だけでなく一般内科外来でも管理を要する“common disease”となることが想像される．本稿では当科で現在進行中の大規模心血管疾患登録観察研究である第二次東北慢性心不全登録研究(Chronic Heart Failure Analysis and Registry in the Tohoku District-2；CHART-2研究，N＝10,219)[3]のデータを紹介しつつ，激増する慢性心不全の将来の患者像を予想し，今後の心不全診療の課題を交えて概説する．

CHART-2研究：概要

CHART-2研究は2006～2010年にかけて東北地方の基幹病院24施設において行われた．適格基準は，①明らかな心不全症状のある患者，②構造的な心疾患を持つが心不全症状のない患者，③すべての冠動脈疾患患者の①～③の少なくとも1つ以上を満たす症例である．すでに10,219例の登録を終了した．現在，予後を前向きに追跡調査中である．平均年齢は68±12歳，男性は約70％である．明らかな心不全患者は46％登録されていた．詳細は文献3を参照いただければ幸いである．CHART-2研究の概要について図1に示す．

将来の日本人の心不全の特徴

1．虚血性心疾患有病者数の増加

生活の欧米化に伴い虚血性心疾患の発症率は増加しているといわれているが，実は虚血性心疾患の発症率について本邦からの報告は少ない．

* Patients with heart failure will increase explosively in the near future.

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1. 参加施設：東北地区24基幹病院
2. 登録対象：すべての慢性心不全患者とそのハイリスク症例を連続登録
3. 登録数：10,219例を登録し現在追跡中
4. 追跡：研究コーディネーターが参加施設を訪問して年に1回データを登録して最低3年間追跡
5. 観察研究に加えて，薬物介入臨床試験を並行して進行

図1　CHART-2研究概要

久山町研究からの報告では，1961～2000年の観察期間において40歳以上80歳未満の群では，虚血性心疾患の発症率には有意な増加を示さず，一方で時代とともに80歳以上の超高齢者において虚血性心疾患の発症率が上昇傾向であったことが報告されている[4]．一方，宮城県での病院ベースの登録研究であるMIYAGI-AMI Registry研究からは，急性心筋梗塞の年齢調整発生率は，1979年には10万人あたり7.4人であったが，2008年には10万人あたり27.0人と30年間で約4倍に上昇していることが報告された[5]．降圧治療は時代とともに普及したにもかかわらず主に高齢者に虚血性心疾患発症率が増加した原因としては，脂質異常症を主とした代謝性疾患の増加によることが考えられる．一方で虚血性心疾患に対する治療の進歩は目覚しく，MIYAGI-AMI Registry研究のデータによると1979年の院内死亡率は20%であったが，2008年の院内死亡率は7.8%と著明に低下しており，時代に伴い急性心筋梗塞の明らかな生命予後改善が報告された．同研究グループは，院内予後改善効果の原因は救急車利用率の向上とPCIの施行率増加であると述べている．このような虚血性心疾患の救命率向上に伴い心不全患者は増加していくと思われる．虚血性心疾患の発症率の変化にはさらなる知見の蓄積が必要であるが，実際に，2006年から循環器内科外来に通院する症例を連続登録しているCHART-2研究では虚血性心疾患症例が45%登録されており，これは2000～2005年にかけて行われた第一次東北慢性心不全登録研究(CHART-1研究)[6]に登録された虚血性心疾患症例25%の約2倍に登録者数が増加していることからも，虚血性心疾患の有病者数増加は明らかである(図2)．

2．高齢者弁膜症の増加

加齢は心不全発症の危険因子である．米国心臓協会の統計によると，65歳以上では1,000人年あたり10人が心不全を発症すると報告されている[9]．この発症者数を単純に2009年の日本人口推計にあてはめると，65歳以上の日本人は約3,000万人であり，1年あたり約30万人の心不全が新規に発症することになる．また，同統計によると心不全発症数は，65歳以上75歳未満では1,000人年あたり15.2人に対して，75歳以上85歳未満では31.7人，85歳以上では65.2人と，加齢とともに指数関数的に増加することが示されており，今後の日本人の超高齢化に伴う75歳以上の心不全患者に対する有効な治療戦略が求められる．75歳以上の心不全患者の特徴を評価するために，以下にCHART-2研究の高齢者心不全の基礎心疾患

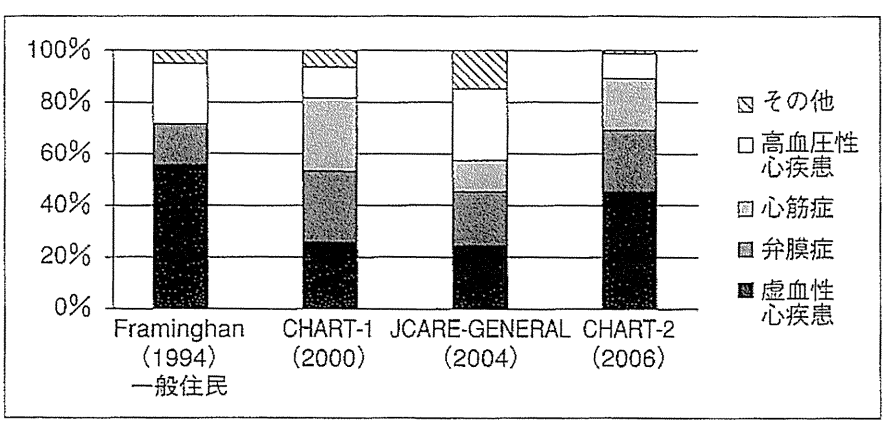

図2　日本人における慢性心不全の基礎疾患の変化：CHART-1/2研究・Framingham研究[7]・JCARE-GENERAL研究[8]の比較

の割合を示す(図3).

図3に示すように，高齢者心不全の基礎心疾患の特徴の一つとして加齢とともに弁膜症が増加することがあげられる．そのため，今後の心不全診療における高齢者弁膜症に対する治療戦略が必要とされる．一方で，高齢者心不全はさまざまな合併症を有するために弁膜症に対する手術不適応例が存在する．心不全に合併する疾患としては貧血・慢性腎臓病・慢性閉塞性肺疾患・睡眠時無呼吸症候群などがあげられるが，これら心不全合併症についての詳細は本誌の他稿をご覧いただければ幸いである．弁膜症に対する薬物治療は経験的に使用されており，evidenceには乏しい．また，物理的な弁の狭窄や逆流に対する薬物療法には限界があり，近年，経カテーテル的治療が導入され日本でも大動脈弁置換術(TAVI)が開始された．すでに先行している欧米から2010年に発表されたPARTNER試験[10]において，症候性の手術適応と判断された高リスク大動脈弁狭窄症に対してTAVIの1年生存率は大動脈弁置換術と同等であったことが示された．本邦では，2010年からTAVIは高度医療として承認されたが，高リスク高齢者の大動脈弁狭窄症に対するきわめて有効な治療法であると期待されている．また，僧帽弁閉鎖不全症に対しても経カテーテル的治療の発展は目覚しい．最近になり僧帽弁閉鎖不全症への経皮的修復術と外科手術の比較を行ったEVEREST II 試験の結果が発表された[11]．重症の僧帽弁閉鎖不全症に対するMitraclip®による経皮的修復術は従来の外科手術と比較し，症状軽減への有効性は低かったが，安全性では優れており，臨床転帰は良好であった．また，EVEREST II 試験のサブグループ解析によれば，70歳未満の症例では外科手術が明らかにより良い臨床転帰をもたらすことが示された一方で，70歳以上の症例において経皮的修復術は外科手術と同等の成績が示された．経カテーテル的治療はlearning curveが存在することや手技に伴う出血や脳梗塞といった合併症，また長期予後がいまだ不明であるなどの問題点があげ

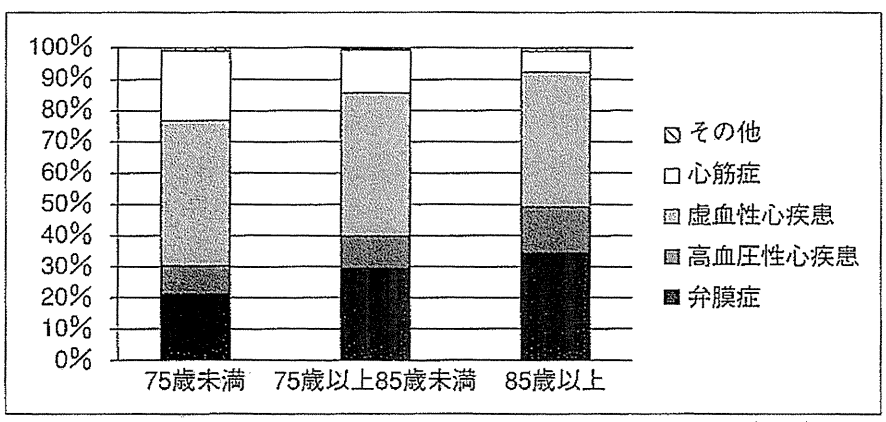

図3 高齢者心不全の基礎心疾患の割合(CHART-2研究より)

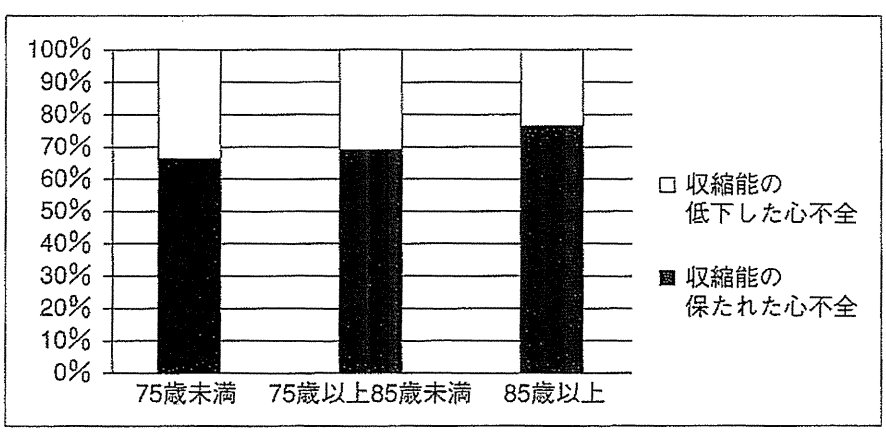

図4 年齢別の収縮能の保たれた心不全の割合(CHART-2研究より)

られるが，外科手術非適応例に対しての経カテーテル的治療は今後ますます日本でも注目されると考える．

3．収縮能の保たれた心不全の増加

2006年にOwanらにより，心不全の約5割を左室収縮能が保たれた心不全(HFPEF)が占め，15年間にわたり左室収縮能の低下した心不全(HFREF)の予後は改善している一方で，HFPEFの予後は改善していないことが明らかにされた[12]．HFPEFの患者背景は多様であり，心不全患者の予後判定を左室駆出率のみで行うことの限界を示していると思われる．HFPEFの診断には統一された定義がないが，その最も重要な臨床的特徴は高齢者が占める割合が多いことである．EFが50%以上をHFPEFと定義しCHART-2研究の心不全患者を分類した図を以下に示す(図4)．日本においても海外と同様にHFPEFは心不全の多くの割合を占め，加齢に伴いHFPEFの症例は増加することが明らかである．

日本人の高齢化に伴いHFPEFの症例は激増することが予想される一方で，HFPEFの予後改善を目的とした大規模臨床試験は，ACE阻害薬であるperindoprilによるPEP-CHF試験[13]，アンジオテンシンII受容体拮抗薬(angiotensin II receptor blocker：ARB)のcandesartanによるCHARM-Preserved試験[14]，irbesartanによるI-PRESERVE試験[15]などが行われてきたが，残念ながらどの臨床試験においても，HFPEFに対するACE阻害薬およびARBの予後改善効果は認められていない．原因としては，現在の心不全診療において多剤併用が行われるために単剤によるHFPEFに対する予後改善効果が併用薬により隠されてしまう可能性がある．また，HFPEFの症例は高齢であるために非心血管死が多いという可能性がある．HFPEFに対するβ遮断薬の有効性に至っては，現在のところ十分な大規模臨床試験がないために降圧目的や洞調律維持目的で使用されており有効性には議論がされている．2013年にはHFPEFに対するspironolactoneの予後改善効果を調べるTOPCAT試験[16]の結果が発表される予定となっている．HFREFに対して予後改善効果が確立されたレニン・アンジオテンシン系抑制薬がHFPEFに対しても有効であるかどうか近いうちに再評価できると期待される．今後，HFPEFに対する薬物治療の次の段階として各薬剤の組み合わせ・各併用薬の至適用量について注目されていくと思われる．

ま と め

本稿では，虚血性心疾患の治療戦略確立による予後改善効果によって虚血性心疾患由来の心不全患者が増加しており，今後もこの傾向は継続する可能性が高いことを述べた．また，高齢化社会に伴い高齢者弁膜症の増加が見込まれること，新しい治療としての経カテーテル的治療の展望につき述べ，最後に収縮能の保たれた心不全の増加と薬物治療の限界につき文献的考察を加えて説明した．日本人の100人に1人が心不全患者であるという来たる時代に備えるために，今後，心不全発症高リスク群に対して心不全発症を予防する観点など，さらなる心不全に対する効果的な治療戦略が必要となってくるであろう．

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話　題

心不全におけるメタボリックシンドロームの重要性*

福本義弘**　下川宏明**

Key Words : chronic heart failure, metabolic syndrome, hypertension, dyslipidemia, diabetes mellitus

はじめに

近年わが国では，食生活の欧米化や運動不足に伴い[1]，メタボリックシンドロームをはじめとする生活習慣病の頻度が増加の一途をたどっている[2]．生活習慣病は心疾患発症のリスクとなり，すでに慢性心不全の始まり(Stage A)と考えられており(図1)，虚血性心臓病や高血圧性心臓病などの発生を通して慢性心不全に至る重要な危険因子である(図2)[3][4]．最近では，若年者でさえ冠動脈硬化症が進展し，虚血性心疾患を有するようになっており，心不全はこれらのあらゆる心疾患の末期像である．現在，わが国における心疾患による死亡率は死因の第2位であることから，まずは生活習慣病の発症予防(早期からの介入)の重要性が指摘されている(図2)．すなわち，食生活を改善し，適度な運動を継続する習慣をつけ，禁煙，塩分制限，飲酒制限に努め，ストレスに関するカウンセリングなどを行い，さらに必要に応じ薬物療法を行うことになる(図1)．なかでもメタボリックシンドロームは，内臓肥満・高血圧・脂質異常症・糖尿病の各因子が，それぞれの程度が軽度ではあるものの，それらが複合して心血管病の成因に深く関係した病態として注目されている(図3)．しかし，その重要性は，虚血性心臓病では広く認識される

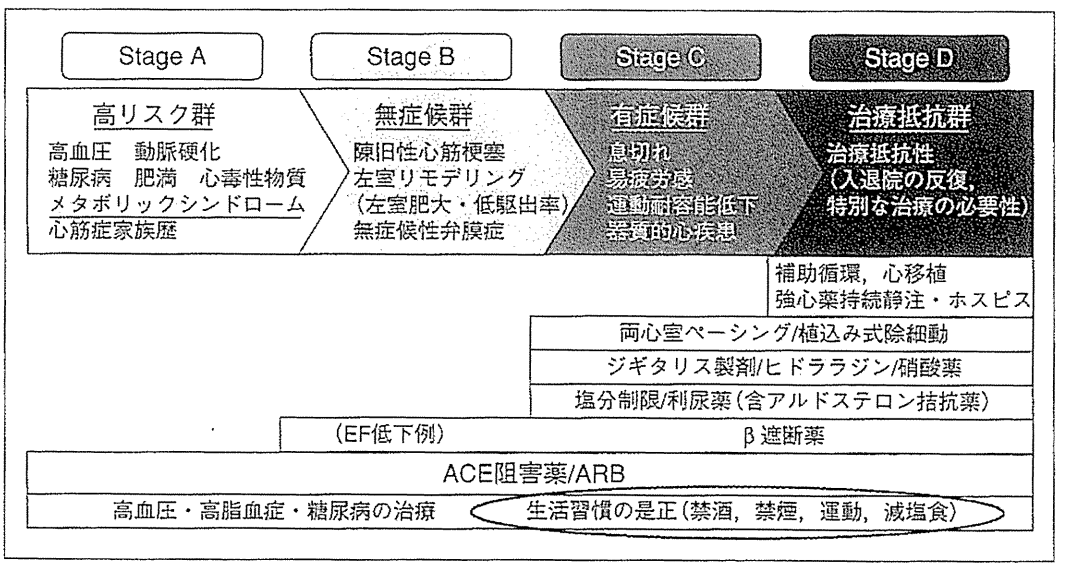

図1　ACC/AHAガイドライン：心不全治療指針

* Important role of metabolic syndrome in chronic heart failure.

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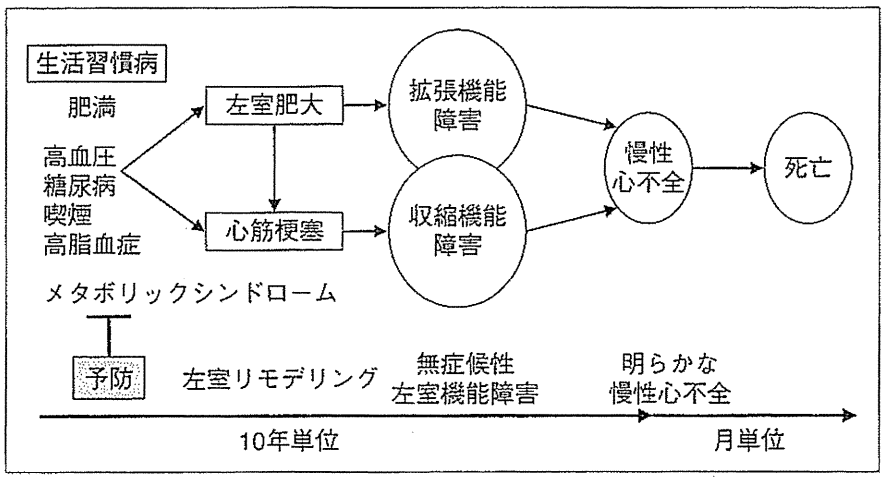


図2　生活習慣病と心血管病の関連(文献[3]より改変引用)

ようになったが[5)~7)]，慢性心不全の発症および進展にどのように関与しているかは明らかではなく，最近検討が行われはじめたばかりである．

メタボリックシンドロームの診断

肥満，糖尿病，脂質異常症，高血圧は代表的な生活習慣病であり，これらの病態は独立して存在することもあるが，1人の患者に重複してみられることが多く，相互に影響しながら動脈硬化を進行させると認識されている．この概念はこれまで，“シンドロームX”や“死の四重奏”といわれてきた病態概念である．わが国ではMatsuzawaが，この病態の根底には内臓脂肪の蓄積が存在するとの概念に基づき“内臓脂肪症候群”として提唱した[8)]．その後，国際組織レベルで統一見解が打ち出され，World Health Organization (WHO)とNational Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATPIII)によるメタボリックシンドローム診断基準が提唱された．わが国でも2005年4月に日本肥満学会，日本動脈硬化学会，日本糖尿病学会，日本高血圧学会，日本循環器学会，日本腎臓病学会，日本血栓止血学会，日本内科学会の8学会が合同でメタボリックシンドローム診断基準を発表した(表1)．この診断基準ではウエスト周囲径が他国のメタボリックシンドローム基準に比べ，男性で小さく，女性で大きい特徴があるが，これは日本人男女を対象とした臍高レベル腹部CTスキャンによって得られた腹腔内脂肪面積100cm^{2}に値するカットオフ値である．このウエスト周

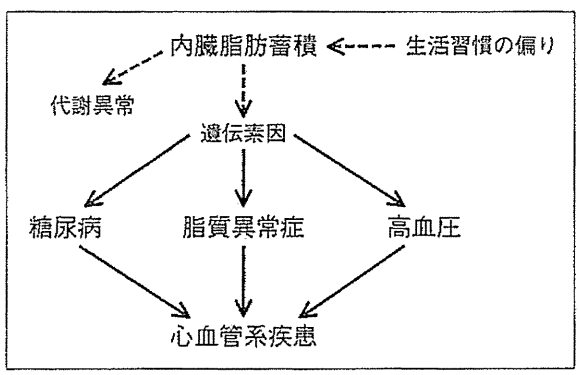


図3　メタボリックシンドロームの概念

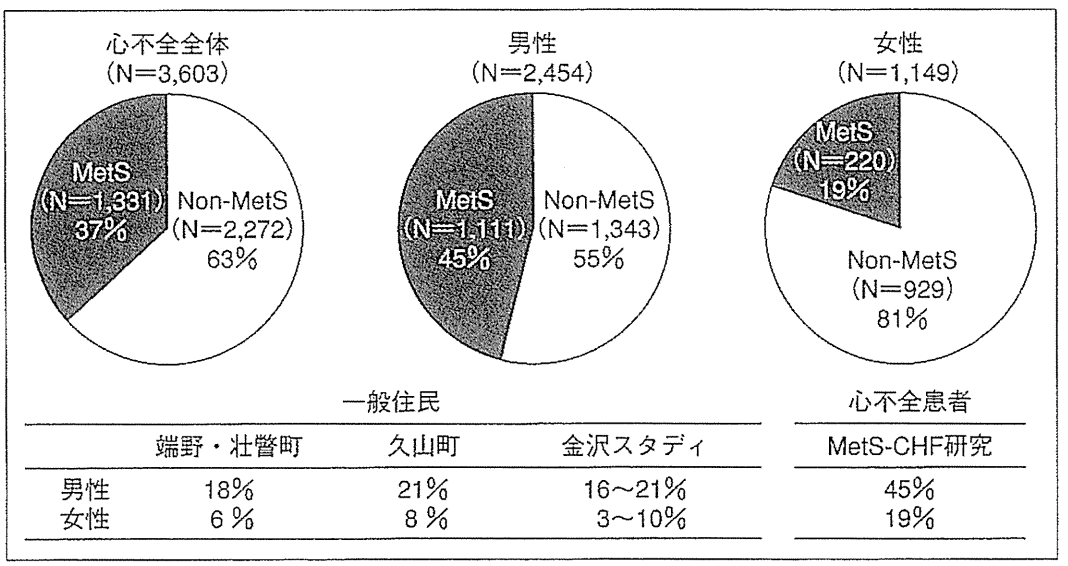
囲径が心血管イベントを予測するかどうか，議論されているところである．後述するデータはわが国のメタボリックシンドローム診断基準に基づくものである．

わが国の慢性心不全に関する疫学データ

わが国では循環器領域における多施設を対象とした疫学研究データが乏しいため，慢性心不全患者の臨床像，治療内容，予後などの実態がわかっていない．欧米で行われた疫学研究があるものの，それらをそのまま人種も年齢構成も異なるわが国の患者にあてはめることができないため，わが国独自の大規模な登録研究が必要である．現在いくつかの心不全コホート研究が進んでいる．九州大学の筒井・竹下らが，福岡市において慢性心不全の診断で入院治療を受けた患者，または内科・循環器科外来で治療を受けている患者を200～400人登録し，予後調査を

表1　現時点でのわが国のメタボリックシンドロームの診断基準

内臓脂肪蓄積	＋	2個以上の危険因子	＝	メタボリックシンドローム
必須項目		3項目中，2項目以上に該当		
ウエスト周囲径 男性 85cm以上 女性 90cm以上	＋	①中性脂肪(トリグリセリド)150mg/dl以上 かつ/または HDL(善玉)コレステロール40mg/dl未満 ②収縮期血圧130mmHg以上 かつ/または 拡張期血圧85mmHg以上 ③空腹時血糖110mg/dl以上		



	一般住民			心不全患者
	端野・壮瞥町	久山町	金沢スタディ	MetS-CHF研究
男性	18%	21%	16～21%	45%
女性	6%	8%	3～10%	19%

図4　慢性心不全患者におけるメタボリックシンドロームの割合
一般人口に比べ，慢性心不全患者でのメタボリックシンドロームの合併率は約2倍である．

行った結果，慢性心不全患者は，従来の大規模臨床試験の対象から除外されてきた70～80歳代が多くを占め，虚血や高血圧を基礎心疾患とし，収縮機能が正常に保たれた患者が30%を占めること，心不全増悪による入退院を繰り返す患者が多いことを明らかにした[9]．さらに，この福岡における研究から，わが国の心不全では虚血性心疾患による心不全が全体の約3分の1であることが示されたが，米国における虚血性心不全の関与は3分の2から4分の3であるといわれており，人種・生活習慣による違いを認めた．また，2000～2003年に当科が中心となって行ったChronic Heart failure Analysis and Registry in the Tohoku district 1(CHART-1 study)では虚血性心不全の関与が25%の頻度であったのに対し，2006年から開始しているChronic Heart failure Analysis and Registry in the Tohoku district 2 (CHART-2 study)では50%近くに激増している[10]ことからも，生活習慣の変化による動脈硬化性疾患の進行を認めている．

わが国の心不全における メタボリックシンドロームの役割に 関する疫学データ

そこで東北大学・下川が班長となり，2006(平成18)～2008(平成20)年度の3年間，全国6施設が参加した厚労省研究班を立ち上げ，「慢性心不全におけるメタボリックシンドロームの意義に関する全国多施設共同研究」(MetS-CHF study)を行った．今回，本研究班のデータベースを用いた中間報告によると，登録された慢性心不全Stage C～Dの患者におけるメタボリックシンドローム合併患者は男性患者の45%，女性患者の19%であり，これはわが国の一般住民におけるメタボリックシンドロームの割合が男性16～21%，女性3～10%と報告されていることから，そ

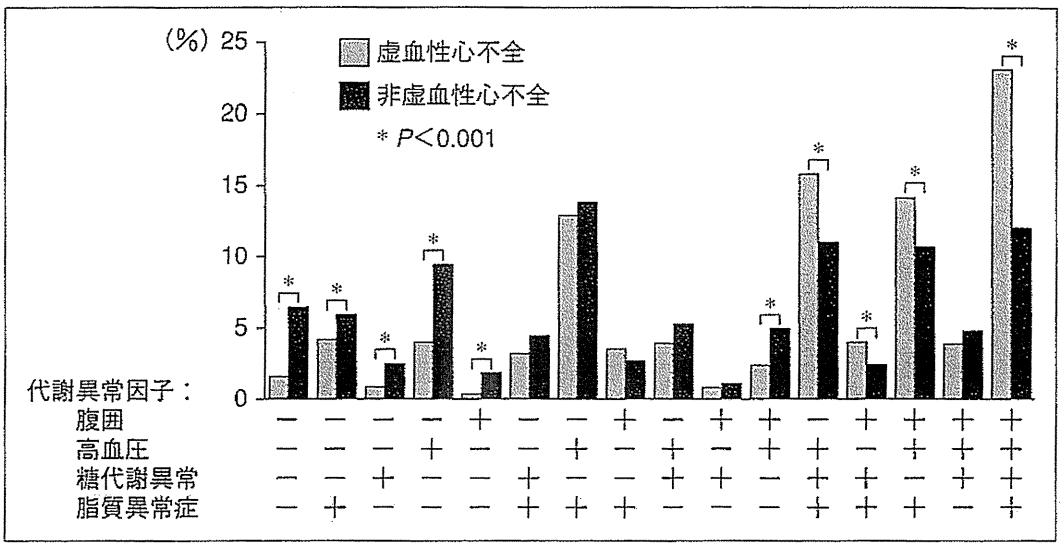


図5　虚血性心不全における腹囲・高血圧・糖尿病・脂質異常症の関与
虚血性心不全では代謝異常症の関与が大きいが，非虚血性心不全においても代謝異常症が関与していた．
（文献[11]より改変引用）

の約2倍の頻度であることが明らかとなった[11]（図4）．またその病態の内訳は，高血圧の合併が91%，脂質異常症が88%，糖尿病が67%と高血圧および脂質異常症の合併頻度が特に高いことも明らかとなり[11]，わが国の慢性心不全において，高血圧，脂質異常症，糖尿病以外にもメタボリックシンドロームが慢性心不全の成因に深く関与している可能性が示唆された．さらに，この研究において，虚血性・非虚血性心不全における個々の代謝異常症を検討したところ，代謝異常症が多いほど虚血性心不全の割合が大きくなるものの，非虚血性心不全においても代謝異常症が関与していることが明らかとなった（図5）[11]．ほかのわれわれの検討から，わが国では急性心筋梗塞の発症率が急増しており，それにはメタボリックシンドロームを構成する危険因子の蓄積が増加していることも明らかとなっている[12]．したがって，虚血性・非虚血性心不全ともに，今後のわが国における慢性心不全に対する治療ターゲットには，高血圧，脂質異常症，糖尿病のみならず，メタボリックシンドロームの加療が重要であると考えられる．

メタボリックシンドロームの治療

メタボリックシンドロームの治療には内臓脂肪の減少が何より重要であり，まず生活習慣の是正が必要である．内臓脂肪減少の薬物は今のところ適切なものがないため，まず食生活を改善し，適度な運動を継続する習慣をつけ，禁煙，塩分制限，飲酒制限に努めることが重要である．

食生活の改善として，野菜，海藻，魚介類などを多く摂取し，肉類は脂肪の少ない鶏肉（皮，卵を除く）や子牛などにし，卵やレバーなどコレステロールの多い食品や飽和脂肪酸の多い乳製品，牛肉などはなるべく避けるといった食事療法を行う．また，運動療法を中心にした心臓リハビリテーションにより活動能力の向上，心筋灌流の改善，治療コンプライアンスの向上，クオリティ・オブ・ライフの改善，心血管系死亡の減少，虚血症状の軽減，粥状硬化の安定化，その後の冠動脈イベントリスクの低下などの効果が期待できるため，最適な運動療法を行う．さらに禁煙指導も非常に重要である（図1）．

メタボリックシンドロームの治療のためには，①適正体重の維持，②バランスの取れた規則正しい食事，③脂肪摂取・塩分摂取・ジュースやお菓子などの糖分摂取の制限，④ウォーキングなどの適度な運動，⑤十分な睡眠・休養，⑥禁煙，⑦適切な飲酒が重要である．その治療を実行するにはまず患者個人の認識が必要で，メタボリックシンドロームは非常に多くの国民が罹患しており，これは動脈硬化性疾患のリスクとなるだけでなく，心不全発症リスクでもあることを認識し，早期の管理が重要であることを知っ

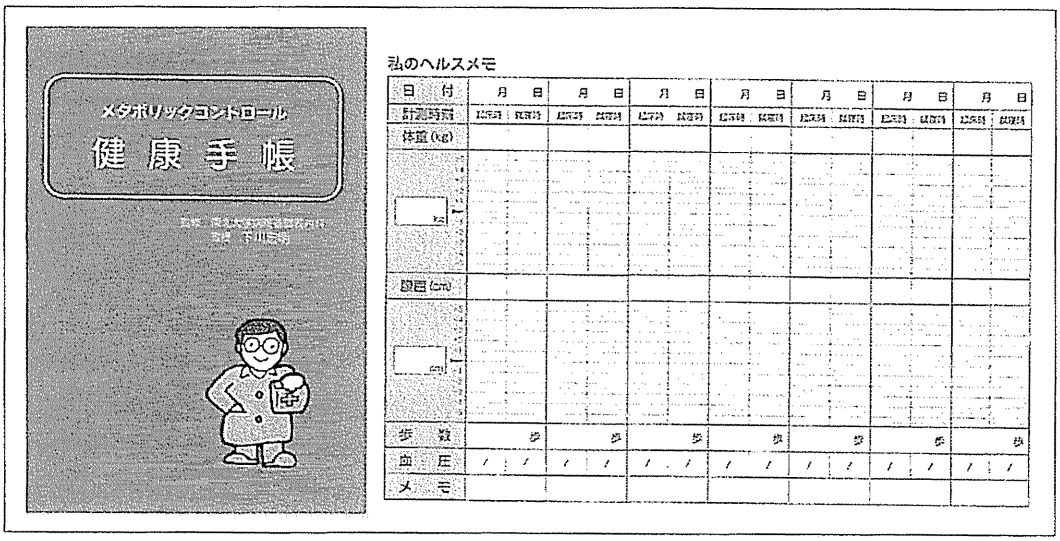


図6　筆者らの使用している健康手帳

ておく必要がある．筆者らは，それぞれの症例において毎日の体重測定・腹囲測定を行い，運動できる患者では万歩計を用いて日常生活における運動量を決定し，健康手帳(図6)をつけることで内臓肥満の是正を図っている．しかしながら，一部の患者では是正されるものの，多くの場合，体重・腹囲のコントロールは不十分であり，近い将来，効果的な治療法の開発が望まれるところである．

内臓脂肪のコントロール以外には，スタチンなどを用いた脂質異常症の改善，降圧薬を用いた至適血圧の維持，抗糖尿病薬を用いた食前・食後血糖のコントロールを行う(図1)．慢性心不全の二次予防には，これらの動脈硬化危険因子のコントロールが非常に重要である．

おわりに

前述のように筆者らは，東北地方における心不全コホートを立ち上げており，1万人規模を登録するCHART-2 studyを開始している．また，全国レベルでも，JCARE-CARD研究，JCARE-GENERAL研究，J-CHF研究などの心不全研究が行われており，それらの結果から，心不全の臨床像と予後との関連，特に治療内容と予後との関連を解析することが可能になり，わが国の慢性心不全患者における予後の規定因子や治療ターゲットの決定，各心不全治療の効果など，きわめて貴重な情報を得ることができると期待される．

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Journal of Cardiology (2011) 57, 8–17

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Review

Chronic kidney disease and heart failure—Bidirectional close link and common therapeutic goal

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Received 9 September 2010; accepted 14 September 2010
Available online 27 October 2010

KEYWORDS
Heart failure;
Kidney;
ACE inhibitor

Summary Chronic kidney disease (CKD) is common and the estimated prevalence is about 9–13% in the general adult population. CKD is defined by the presence of kidney damage or decreased glomerular filtration rate. Individuals with CKD have a far greater likelihood of cardiovascular death than progression to end-stage renal disease. Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder and the prevalence is reported to be 2–3% in the general population. The prognosis of HF patients is still poor despite recent advances in HF treatment. Both diseases are major and growing public health problems because aging of the population contributes to the increasing incidence of those diseases. More than 40% of HF patients have CKD and the close relationship between CKD and HF worsens their prognoses. All physicians must evaluate kidney function using estimated glomerular filtration rate calculated by the new Japanese equation in patients with HF. Accurate evaluation of pathophysiology between the two diseases and appropriate intervention are necessary to improve the prognosis of patients with the diseases.

Contents

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Introduction

Chronic kidney disease (CKD) is an extensive public health problem which should be recognized properly by every healthcare provider. The US National Kidney Foundation Kidney Disease Outcome Quality Initiative proposed the concept of CKD and established the definition and classification in 2002 [1].

Studies from the USA, Europe, Australia, and Asia showed that the prevalence of CKD is about 9–13% in the general population [2–5]. The incidence and prevalence of patients with CKD including end-stage renal disease (ESRD) have doubled in the past 10 years in the USA [6]. Many patients with CKD die from cardiovascular disease (CVD) and patients who need renal replacement therapy are fewer, except in those with ESRD [7]. CKD is more prevalent in patients with CVD or with CVD-related risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome. Furthermore, CKD is a significant aggravating factor in patients with these conditions and is also an important prognostic risk for them [8].

Heart failure (HF) is also a serious and expanding public health matter and is one of the leading causes of mortality in most developed countries. More than 5 million patients have HF and over 550,000 patients are newly diagnosed with HF every year in the USA [9]. The European Society of Cardiology reports that there are at least 15 million patients with HF in 51 European countries, which have a total population of more than 900 million [10]. The prevalence of HF is approximately 2–3% and rises sharply in elderly populations, and it has been increasing because of the progressive aging of the population and the decreased mortality of patients who survived the first coronary event [11]. The total estimated costs for managing HF were reported to be 27.9 billion dollars in the USA in 2005, and 905 million pounds in the UK in 2000 [11,12]. Approximately 50% of HF patients die at 4 years and 40% of admitted patients with HF are dead or readmitted within 1 year despite the recent improved treatment for HF [10].

Patients with HF usually have much co-morbidity such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia, cachexia, gout, and renal insufficiency, and such co-morbidity aggravates the condition of HF. Renal dysfunction is especially common in HF patients, and anemia, hyperkalemia, low serum albumin, and uses of renin-angiotensin-system (RAS) inhibitors, aldosterone antagonists, and diuretics are associated with such disorder [10]. The prevalence of renal impairment increases with age, HF severity, a history of hypertension, or diabetes.

Such close interaction between kidney and heart has been called "cardiorenal syndrome (CRS)" and this connection is observed to be the most strong in patients with HF. It seems to be mediated by not only the decreased cardiac output but also by the effects of the activated RAS, the imbalance between nitric oxide and reactive oxygen species, inflammation, anemia, and the increased sympathetic nervous activity.

This brief review describes the close relationship and pathophysiology between CKD and HF, and summarizes treatment strategies in HF patients with CKD.

Table 1 Definition of chronic kidney disease [1].

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: Pathological abnormalities; or Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR < 60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage

GFR, glomerular filtration rate.

Definitions of CKD and HF: progressive disorders

The diagnosis of CKD is easily given by the existence of kidney damage or decreased glomerular filtration rate (GFR) for three months or more. GFR is estimated using the formula including serum creatinine level, age, sex, and ethnicity irrespective of cause of the disease. The definition and classification stages of CKD are shown in Tables 1 and 2 [1]. CKD is considered to be a disease that progresses from mild to

Table 2 CKD classification based on severity [1].

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

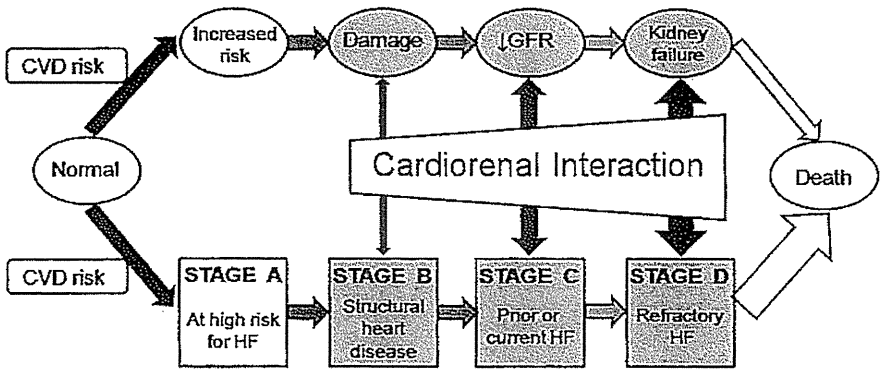

Figure 1 Cardiorenal interaction and stage classification in the initiation and progression of chronic kidney disease and heart failure [1,11]. CVD, cardiovascular disease; HF, heart failure; GFR, glomerular filtration rate.

severe condition as shown in Fig. 1, which is the conceptual model of the course of CKD.

HF is a complex clinical syndrome that can be caused by any structural or functional cardiac disorder that impairs the pump function of the heart [11]. There have been many definitions of HF proposed to date [13]. The common and most important feature of HF syndrome includes symptoms, signs, and objective evidence of a structural or functional abnormality (Table 3). It must be emphasized that HF is not equal to left ventricular dysfunction and HF is characterized by specific symptoms in the past medical course and signs revealed by the physical examination. The Writing Committee of the AHA/ACC Heart Failure Guidelines developed a new stage classification of HF in 2001, which includes 4 stages presenting the development and progression of the HF syndrome (Fig. 1). Stage A denotes patients with CVD risks such as hypertension, diabetes mellitus, metabolic syndrome, etc. and without any geometric or functional disorder in the left ventricle. In contrast, patients who are asymptomatic but show left ventricular hypertrophy and/or left ventricular dysfunction are indicated as Stage B. When patients have symptoms of HF caused by underlying structural heart disease in the current or past medical status, those are considered to reach Stage C. Finally Stage D specified patients with refractory HF who may need mechanical circulatory support or heart transplantation [11].

Table 3 Definition of heart failure [10].

Heart failure is a clinical syndrome in which patients have the following features:
Symptoms typical of heart failure
(breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)
and
Signs typical of heart failure
(tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly)
and
Objective evidence of a structural or functional abnormality of the heart at rest
(cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Both classifications of CKD and HF have the same characteristics which clearly show the progressive manner of diseases and these classifications can provide a reliable and objective tool to identify patients on the way of developing the diseases (Fig. 1). Furthermore, they can indicate the recommendation for treatments which are considered to be appropriate at each stage of illness and are expected to prevent advancement from one stage to the next.

Patients in the clinical intersection between CKD and HF are at a high risk for poor outcomes. Inter-relationships of CKD and HF include common characteristics, such as common risk factors, bidirectional effects of one disease process on the progression of the other, adverse effects on one disease process when investigating the other, and treatment biases potentially influenced by both diseases. Those clinical and pathophysiological links will be more expanded as the stage progresses and will aggravate the severity of the diseases more seriously (Fig. 1).

HF in patients with CKD

The overlap between CKD and other chronic diseases, most notably diabetes, hypertension, chronic obstructive pulmonary disease, and CVD is common. The annual data report of the United States Renal Data System (USRDS) in 2009 reported that the prevalence of CVD reached 63% in CKD patients compared to 5.8% of those without CKD, and it graded the association with both CKD severity and age [6]. While CKD is a risk multiplier for the development of CVD, the largest hazard occurs for HF. Compared with patients without CKD, the relative risk for the development of HF was 1.45 and 1.68 in patients with CKD of stage 1–2 and 3–5, respectively, when evaluating Medicare patients age 66 and older [6]. The event rate of HF diagnosis in those patients was the highest among all CVD and it was 56 events per 1000 patient years for patients without CKD and 176 for those with CKD of stage 3–5. Age-adjusted survival of CKD patients with HF was poor; one-year mortality of patients with CKD of stage 3–5 was nearly 25% although that of those without CKD was 17% [6].

Table 4 Prevalence and hazard of chronic kidney disease in patients with chronic heart failure.

Ref. no.	Study	Year	No. of pts	NYHA	Age, years	Male, %	EF, %	BP or HTN	DM, %	RASi, %	eGFR < 60,%	Follow-up	Outcome	Adjusted hazard comparing with pts without CKD for the outcome
17	SOLVD-T	2000	2,161	I–IV	60.7	81.5	24.7	40.4%	24.9	50.3	35.7	–	All-cause mortality	1.41 for eGFR <60[a]
18	PRIME-II	2000	1,906	III–IV	64.7	80.4	26.2	121.6/ 75.1 mmHg	20.7	91.6	49 (eGFR ≤ 58)	277 days (median)	All-cause mortality	1.91 for eGFR 44–58 2.85 for eGFR <44
19	DIG	2002	585	II/III: 85%	65	73.9	35	128.3/ 75.3 mmHg	40.3	88	50 (eGFR ≤ 63.8)	2.6 years (median)	All-cause mortality	1.6 for eGFR 47–64[a] 2.1 for eGFR 18–48[a]
20	McClellan	2002	665	–	75.7	40	38.4	66%	44	54	38[b]	–	All-cause mortality	1.24 at 1-year mortality[b]
21	UK-HEART	2002	553	II/III: 98%	62.7	76	42	–	0	82	–	–	All-cause mortality	1.09 in each 10 μmol/l increase of creatinine
22	CHARM	2006	2,680	II–IV	65.3	66.6	38.5	128.2/ 73.6 mmHg	37.2	45.5	36	34.4 months	CV death + HF hospitalization	1.54 for eGFR 45–59.9 1.86 for eGFR <45
23	ANCHOR	2006	59,772	–	71.8	54.2	NA	61%	32.4	24	39.2	2.07 years (median)	All-cause mortality + HF hospitalization	1.39 for eGFR 30–44 2.28 for eGFR 15–29
24	CHART	2008	920	II–IV	68.3	65.1	49.3[c]	39.2%[c]	19.3[c]	69.1[c]	42.7	3.45 years	All-cause mortality + HF hospitalization	1.31 for eGFR 30–59 1.56 for eGFR <30
25	JCARE-CARD	2009	2,013	1.8 (mean)	71.5	58.7	44.8	54.5%	30.7	ACEi: 36.7 ARB: 46.1	70.3	2.4 years	All-cause mortality	1.26 for eGFR 30–59 2.48 for eGFR <30

EF, ejection fraction; BP, mean blood pressure; HTN, hypertension; DM, diabetes mellitus; RASi, renin–angiotensin-system inhibitor; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); pts, patients; CKD, chronic kidney disease; HF, heart failure; CV, cardiovascular; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] ml/min.

[b] CKD was defined by serum creatinine of ≥1.4 mg/dl for women and ≥1.5 mg/dl for men.

[c] Data were retrieved from the previous study that included 1154 patients.

Unadjusted all-cause mortality evaluating Medicare patients age 66 and older showed the declining trend in patients with CKD during the past 10 years. However, relative risk of mortality was almost 3 times higher when CVD accompanied CKD [6]. Approximately 50% of CKD patients died of complications of CVD before they reached ESRD [14]. Keith et al. revealed that death was more common than progression to ESRD by evaluating more than 28,000 patients with CKD from a health maintenance organization [7]. Only about 20% of patients with stage 4 CKD had progressed to dialysis, whereas 46% had died of cardiovascular complications.

CVD accounted for 43.7% of the all-causes of death in dialysis patients in the USRDS database in 2005–2007 [6]. The percentage of HF as a cause of mortality was 5.3%, however event rates for congestive HF in dialysis patients reached 270 per 1000 patient years [6]. A report from the HEMO study indicated that HF prevalence in ESRD patients is about 40% [15].

The prevalence and incidence of HF, and the percentage of mortality due to HF in patients with mild to moderate CKD is not well described, because such patients have a broad spectrum of characteristics including CKD stage, age, and cardiovascular risks. Kottgen et al. studied the role of impaired kidney function as a risk factor for incident HF evaluating 14,857 middle-aged individuals without HF who were enrolled in The Atherosclerosis Risk in Communities Study [16]. Crude HF incidences were 5.7, 5.9, and 17.7 per 1000 person-years in those with estimated GFR $\geq$ 90, 60–89, and <60 ml/min/1.73 m^2, respectively, and a greater decline in kidney function during the follow-up period occurred in individuals concomitant with HF hospitalization/death compared to those who did not develop HF.

CKD in patients with HF

CKD is common in patients with HF. Table 4 shows the major publications including our report describing the prognosis and characteristics of chronic HF patients with CKD that were published after 2000 [17–25]. CKD was present in 35–70% of HF patients evaluated in cohort studies or subanalyses of randomized controlled trials. Furthermore, the comorbidity of CKD was associated with increased hospitalization due to worsening HF and all-cause/cardiovascular deaths. The hazard ratio for all-cause mortality in HF patients with moderate to severe CKD was about 1.3–2.9 compared to those without CKD (Table 4). The prognostic impact of CKD was observed in a broad spectrum of HF patients [22], however Ahmed et al. reported accompanying CKD was more strongly associated with mortality in patients with preserved ejection fraction than in those with reduced ejection fraction [26].

One of the major mechanisms of worsening renal function in patients with HF is considered to be long-term reduced renal perfusion. However, estimated GFR in HF patients with preserved ejection fraction was similar compared with that in those with reduced ejection fraction [27] and the ESCAPE trial revealed that renal congestion might be a more important factor for renal impairment compared to increased pulmonary artery pressure [28]. Other contributing factors of hypoperfusion are the increased vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and pharmacotherapy-related effects including diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension [29]. Other possible mechanisms of kidney–heart interaction are shown in Table 5.

Table 5 Proposed mechanism in cardiorenal interaction.

Common factors for heart and kidney	
Traditional cardiovascular risk factors	
	Smoking
	Obesity
	Hypertension
	Diabetes
	Dyspilidemia
Other risk factors	
	Malnutrition
	Genetic risk factors
Humorally mediated factors	
	Elevated sympathetic nervous system
	Elevated renin-angiotensin system
Other common factors	
	Inflammation
	Endothelial dysfunction
	Immune mediated damage
	Oxidative stress
	Coagulation imbalance
Treatment related factors	
	Undertreatment
	Toxic agents
Organ-specific factors	
Hemodynamics mediated factors	
	Decreased cardiac output (heart)
	Renal hypoperfusion (heart)
	Elevated venous pressure (heart)
	Sodium and water retention (kidney)
	Hypertension (kidney)
Other specific factors	
	Brain natriuretic peptide (heart)
	Anemia (kidney)
	Uremic solute retention (kidney)
	Calcium and phosphate abnormality (kidney)
	Electrolyte, acid-base imbalances (kidney)

Acute kidney injury in patients with acute heart failure

Acute heart failure (AHF) is defined as a rapid onset or change in the signs and symptoms of HF, which may be either new HF or worsening of pre-existing chronic HF. Although AHF is usually characterized by pulmonary congestion, acutely reduced cardiac output and tissue hypoperfusion are also important hemodynamic aspects, which sometimes cause multiorgan failure. A rapid worsening of cardiac function also leads to acute kidney injury

Table 6 Proposed definitions of cardiorenal syndrome [34].

CRS type I (acute CRS)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

CRS, cardiorenal syndrome.

(AKI) and pre-morbid chronic renal dysfunction has been reported as a common precursor for AKI in HF patients [30,31]. Worsening renal function, defined as a rise in serum creatinine level >0.3 mg/dl, during hospitalization for HF is observed in 20–30% of HF patients [29]. Any change in serum creatinine has been reported to be associated with longer hospital stay, increased costs, and increased short-term/long-term mortality [29]. Lower estimated GFR on HF admission was also an independent predictor for long-term mortality in AHF patients [32]. The mechanisms of the relationship are multiple and complex including persistent vasoconstriction, high renal venous pressure, elevated intra-abdominal pressure, adenosine and tubuloglomerular feedback, and medicine perturbing intrarenal hemodynamics (Table 5) [29,33].

Classification of cardiorenal syndrome

The bidirectional natures of heart and kidney interaction represent the pathophysiological basis for a clinical entity that has been called cardiorenal syndrome (CRS) (Fig. 1). Ronco et al. proposed the new classification of CRS to help physicians characterize groups of patients, to provide the rationale for specific management strategies, and to allow the design of future clinical trials [34]. They defined CRS as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other, and divided CRS into 5 different subtypes (Table 6). The proposed mechanism of kidney–heart interaction is also shown in Table 5. The benefit and validity of using this classification should be confirmed in future studies.

Anemia in patients with CKD and/or HF

Anemia develops relatively early in the disease course of CKD and worsens with CKD severity. McClellan et al. reported that anemia was present in 47.7% in 5222 enrolled patients with CKD [35] and the prevalence of anemia was strongly associated with decreased GFR. The major mechanisms of the development of anemia are decreased erythropoietin production and increased erythropoietin resistance, and other causes include decreased red blood cell life span due to uremic toxins, chronic blood loss caused by platelet dysfunction, nutritional deficiencies [36], iron deficiency, and elevated inflammatory cytokines [37] that may cause bone marrow suppression.

Anemia also frequently occurred in HF patients, with reports ranging widely from 9.0% to 79.1% [38,39], but the majority of studies described more than 20% [40]. Previous reports suggested that decreased hemoglobin level was associated with increased rates of death and HF-related admission [23]. Anemia observed in HF patients mainly is attributed to kidney-related factors described above, and is also related with bone marrow suppression by frequent angiotensin-converting enzyme (ACE) inhibitor use in HF patients [41]. Because CKD and anemia frequently co-exist and worsen the prognosis in patients with HF, CRS is also named as "cardio-renal-anemia syndrome" [40].

Whether the correction of anemia using erythropoiesis-stimulating agents is beneficial or not in patients with CKD or HF is still controversial. Previous trials have reported that the complete normalization of hemoglobin levels in CKD patients did increase adverse outcomes, although it might improve cardiac function [42]. The CHOIR study revealed the surprisingly higher rates of adverse events in CKD patients targeted for the high hemoglobin level (13.5 g/dl) compared with those in the low hemoglobin group (11.3 g/dl) [43]. The CREATE and the TREAT studies also showed that the complete correction of hemoglobin level did not demonstrate any improvement in cardiovascular events [44,45]. Meanwhile, some previous studies evaluating patients with HF showed a beneficial impact of anemia correction on HF symptoms, left ventricular ejection fraction, and quality of life [46,47]. However, in a recent trial in HF patients (STAMINA-HeFT), darbepoetin alfa treatment did not significantly improve exercise duration, NYHA functional class, or even health-related quality of life [48]. A large-scale, double-blind, randomized morbidity and mortality trial (RED-HF) is currently ongoing and it may demonstrate the impact of anemia correction on mortality in those patients [49].

Treatments of CKD patients with HF and of HF patients with CKD

A complete description or details of treatment in patients with CKD or HF are beyond the scope of this article, which may appear in the authoritative clinical practice guidelines for the treatment of CKD or HF [1,10,11]. The following part highlights the issue regarding the treatment using RAS inhibitors, which is the most commonly recommended therapy in patients with HF or CKD.