特集 糖尿病と精神疾患

糖尿病と精神疾患の疫学

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はじめに

精神的な健康が保たれていることは，糖尿病を良好に管理する上で重要である。というのも精神医学的な問題を抱えている患者やその家族では，糖尿病を治療する上で求められる療養行動の遂行が阻害される結果，より良い健康予後を達成するのが困難になる場合が少なくないからである。これを受けて，わが国の「糖尿病治療ガイド」をはじめ各ガイドラインでは，患者の心理社会的な状況を適宜評価することを推奨している[1)2)]。

糖尿病診療従事者が精神医学的な問題を抱える患者を診療するケースとしては，糖尿病と診断されることや生活習慣の変更を強いられることなどを契機に不安や抑うつ症状を訴えるようになる場合や，糖尿病の経過中に，糖尿病とは独立に何らかの精神疾患を発症する場合など，糖尿病診療従事者が発見して精神保健医療の窓口に紹介する場合と，精神科や心療内科での治療経過中に耐糖能異常を指摘され糖尿病外来を紹介受診される場合とが考えられる。本稿では，それぞれの場合における糖尿病と精神疾患との関係について，現在得られている疫学知見を紹介する。

Ⅰ．わが国の精神疾患の疫学

初めに，主な精神疾患のうち糖尿病との関連が報告されているものについて，わが国における現状を確認しておく（図1A）。

統合失調症は，厚生労働省の2011年患者調査によると，ある1日に統合失調症あるいは統合失調症型障害および妄想性障害で国内の医療機関を受診した患者数が23.5万人で（入院17.4万人，外来6.1万人），そこから推計される受診中の患者数は71.3万人とされている[3)]。また世界各国からのデータに基づく系統的レビューでは，統合失調症の生涯有病率は人口の0.7%，1年間の新たな発症が人口10万人あたり15人と報告している[4)5)]。

気分障害のうち，双極性気分障害の頻度は1型，2型を合わせて人口の0.7%程度とされている。一方単極性のうつ病は，DSM-Ⅳ（Diagnostic and Statistical Manual of Mental Disorders, 4th Edition）を用いた平成18年度厚生労働科学研究で，生涯有病率が6.3%，12ヵ月有病率は2.1%であったと報告されている[6)]。患者調査の結果からは，うつ病の推計患者数が1996年には27.2万人であったのが，2011年には70.1万人と著しく増加している点が注目されている（図2）[3)]。

同じく，平成18年度厚生労働科学研究内で不安障害の頻度が報告されている[5)]。これによると，何らかの不安障害を有するものの生涯有病率は9.2%，12ヵ月有病率では5.5%に上るとのことである。

摂食障害については，1998年に全国の医療施設（23,401施設）を対象に実施された中枢性摂食異常調査研究班の全国疫学調査が報告している。これによると，患者推定数（罹患率）は神経性食思不振症が12,500（人口10万対10.0），神

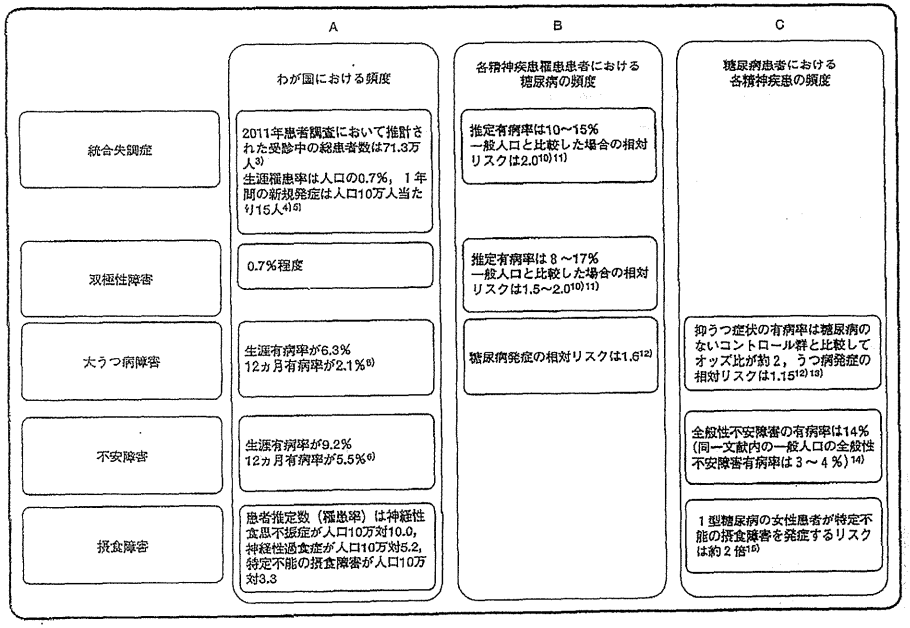

図1．わが国における精神疾患の頻度と糖尿病との関係

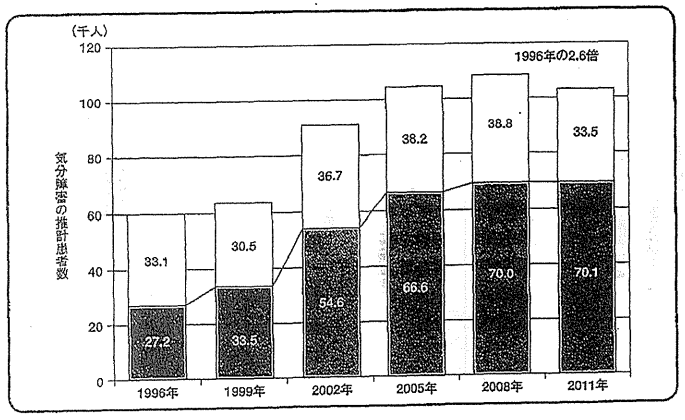

図2．うつ病の推計患者数

□：双極性障害，気分変調症，その他，■：うつ病*

*うつ病の患者数はICD-10におけるF32（うつ病エピソード）とF33（反復性うつ病性障害）を合わせた数

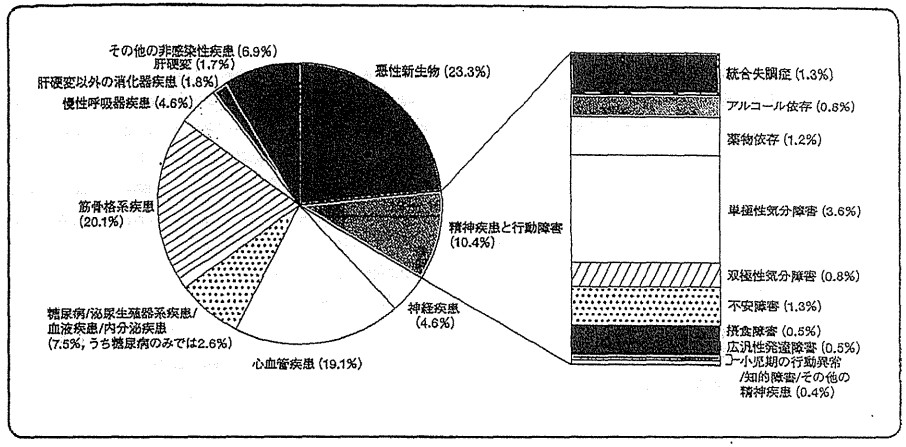

図3．わが国のDALYsに対する各非感染性疾患の寄与度

DALYsとは「早死によって失われた潜在的な年数の概念を拡張して，損なわれた健康や障害のために失われた健康的な生活の年数も含めた」健康指標であり，死亡者数のみではとらえられない疾病負担を定量的に評価できる。DALY1単位は「健康な1年間」の損失を意味し，「早死損失年数（Years of life lost：YLL）」と「障害共存年数（Years of life with disability：YLD）」から構成される。

日本におけるDALYsへの寄与度は感染性疾患が6.9%，非感染性疾患が83.5%，外傷が9.6%である。本図では非感染性疾患全体を100%とした場合に，非感染性疾患内のそれぞれの疾患に起因するDALYsをパーセントで表している。

経性過食症が6,500（人口10万対5.2），特定不能の摂食障害が4,200（人口10万対3.3）であった。摂食障害は近年わが国での患者数が急増しているだけでなく，患者層が若年化していることも問題である。

ところで前述の精神疾患，および糖尿病や糖尿病に関連する身体疾患は，日本人の健康障害や死亡にどの程度寄与しているのであろうか。ここで注目すべきは，いずれの疾患も死亡のリスクが高まるだけではなく，発症や病気の進展によって引き起こされる障害のために長期間にわたって健康寿命が障害されるという共通点があることである。Institute for Health Metrics and Evaluation（IHME）が報告しているGlobal Burden of Disease（GBD）Study 2010によると，障害調整生存年数（disability-adjusted life-years：DALYs）でみた場合に，日本人の全DALYsのうち83.5%は非感染性疾患が占めている（図3）[7]。この内訳をみると，非感染性疾患全体を100%とした場合に悪性新生物が最も寄与度が高く23.3%で，第3位が心血管疾患（19.1%），第4位が精神疾患と行動障害（10.4%）となっている。なお，糖尿病の寄与度は2.6%である。精神疾患と行動障害のなかでは，単極性気分障害の寄与度が最も高く（3.6%），ついで統合失調症（1.3%），不安障害（1.3%），薬物依存（1.2%），アルコール依存（0.8%），双極性気分障害（0.8%）と続いている。

次いでDALYsの主要疾患のうち上位25疾患を，1990～2010年にかけての変化量とともに図4で示す。これによると脳卒中と虚血性心疾患が2位と3位を占め，糖尿病が14位，精神疾患中では大うつ病性障害が12位，不安障害と統合失調症が23位と24位を占めている。これらの疾患は虚血性心疾患以外，1990年と比較してDALYsや順位に大きな変化はない。DALYsと早死損失年数（Years of life lost：YLL）の主要疾患の順位を比較した場合，脳卒中と虚血性心疾患はYLLの1位と2位でDALYsと順位はそれほど変わらないが，糖尿病の順位はYLLの27位，統合失調症，大うつ病性障害，不安障害に至っては76位以上と大いに寄与度が低下する。この報告から，糖尿病と精神疾患は生存者における障害の程度が大きい疾患であることがわかる。

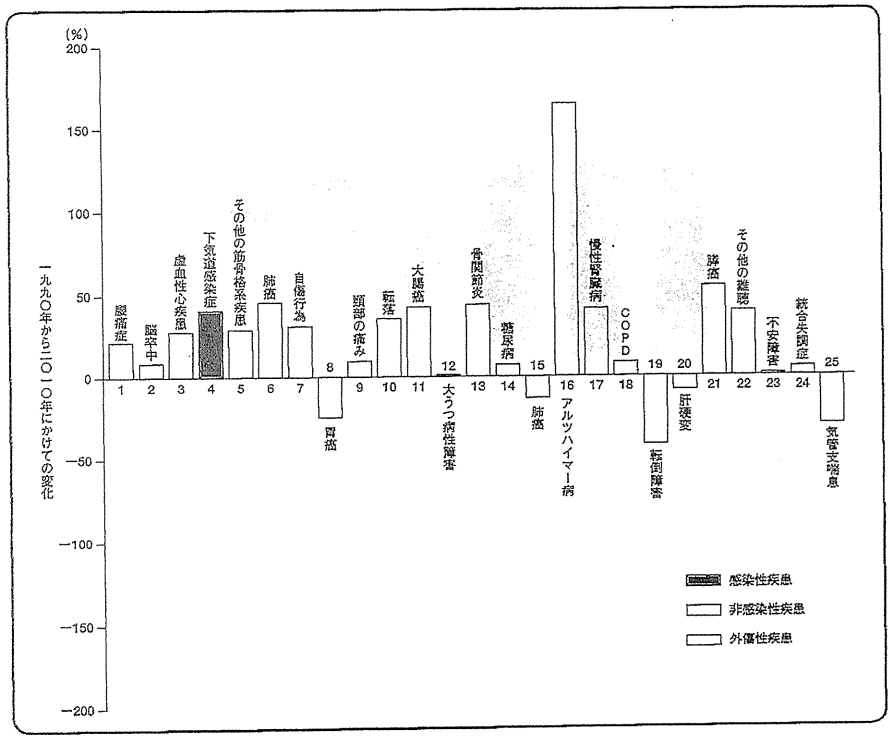

図4．わが国のDALYsの主要因と1990年から2010年にかけての変化率

DALYsの主要疾患のうち上位25疾患を示している。
上向きのバーはその疾患によるDALYsが1990年と比較して増加したことをパーセントで示している。
反対に下向きのバーはその疾患によるDALYsが1990年と比較して減少したことをパーセントで示している。

（文献7より引用改変）

Ⅱ．糖尿病と精神疾患の疫学

統合失調症や双極性気分障害，大うつ病性障害などに代表される比較的重篤な精神疾患（severe mental illness：SMI）に罹患している患者では，糖尿病やメタボリック・シンドロームの有病率が高いことが報告されている（図1B，表）[8)-11)]。海外からのデータに基づく報告では，統合失調症患者と双極性気分障害患者における糖尿病の推定有病率はそれぞれ10～15%と8～17%，一般人口と比較した場合の相対リスクはそれぞれ2.0と1.5～2.0であると報告している。大うつ病性障害については，前向き縦断研究に基づくメタ解析の結果から，糖尿病発症の相対リスクは1.60（95% CI：1.37-1.88）と報告されている[12)]。

一方で糖尿病の治療経過中に，うつ病や不安障害などの精神疾患を発症することも報告されている（図1C）。糖尿病患者における抑うつ症状の有病率は，糖尿病のないコントロール群と比較してオッズ比が約2倍であり[13)]，前向き

表．統合失調症，双極性気分障害と心血管疾患危険因子との関係

心血管疾患のリスク因子	統合失調症		双極性障害	
	有病率	相対リスク	有病率	相対リスク
喫煙	50～80%	2～3	54～68%	2～3
脂質異常	26～69%	≦5	23～38%	≦3
高血圧症	19～58%	2～3	35～61%	2～3
肥満	45～55%	1.5～2	21～49%	1～2
メタボリック・シンドローム	37～63%	2～3	30～49%	2～3
糖尿病	10～15%	2	8～17%	1.5～2

（文献9より引用改変）

縦断研究に基づくメタ解析の結果からはうつ病発症の相対リスクが1.15（95% CI：1.02-1.30）とわずかではあるものの有意に上昇していたことが報告されている[12)]。糖尿病患者ではまた，全般性不安障害の有病率が14%（同一文献内の一般人口の全般性不安障害有病率は3～4%）と増加していることも報告されている[14)]。さらに1型糖尿病に罹患した思春期の女性患者では，同年代の女性と比較して約2倍摂食障害に陥る割合が高いことが報告されている[15)]。そしてこれらの精神疾患のうち，うつ病はその発症において糖尿病との間に双方向性の関係があると考えられている。

糖尿病や肥満とSMIを結ぶ要因としてSMI患者における①遺伝学的共通性，②視床下部-下垂体-副腎皮質系の調節障害，③交感神経系の賦活，④精神症状による身体活動の低下や健康的な生活への関心の低下，⑤向精神薬の影響があると想定されており，これらが単独，あるいは複合的に作用して肥満，耐糖能異常を惹起すると考えられている[16)]。

Ⅲ．精神疾患と心血管疾患

SMI患者は，一般人口と比較して標準化死亡比（standardized mortality rate：SMR）が高く，寿命に換算すると20～30年短いことが知られている[17)]。これはSMI患者において自殺率が高いことのみによるのではなく，予防や治療が可能な身体疾患，なかでも心血管疾患による死亡率が一般人口と比較して高いことによる。英国で行われた後ろ向きコホート研究によると，一般人口と比較した統合失調症患者の全死因に基づくSMRの中央値は2.58（95% CI：1.18-5.76）［うち自然死が2.41（95% CI：0.99-4.10），横死が7.5（95% CI：5.56-12.73）］であった[18)]。死因となった疾患別に年齢層別解析をしたところ，虚血性心疾患によるSMRは一般人口と比較して統合失調症患者群で18～49歳が約3倍，50～75歳が約2倍，脳卒中によるSMRは75歳未満で約2倍とそれぞれ上昇しており，心血管疾患死は特に比較的若年層において一般人口との乖離が大きかったことが報告されている。しかもこの乖離は，1987年以降年が下るごとに大きくなっていると考えられている。同様の結果は気分障害患者においても報告されている[19)20)]。

このようにSMI患者で心血管疾患死の危険が高くなる要因として，前述したようにSMI患者で糖尿病の有病率が高いことに加えて，その他の心血管疾患危険因子である肥満，高血圧症，脂質異常症，喫煙などの保有率も高いことがあげられる（表）。SMI患者において心血管疾患や早すぎる死の危険が高まっていく様子は，"メタボリック・ハイウェイ"や"滑りやすい坂"と表現されており[21)]，早い段階で危険因子を特定し，動脈硬化の進展を抑制することが求められている。

一方で，抑うつ症状を有する糖尿病患者においても，総死亡ならびに心血管疾患死の危険が高まることが系統的レビューとメタ解析で報告されている[22)]。これによると，抑うつ症状を有する糖尿病患者の総死亡のハザード比は抑うつ症状を有さない糖尿病患者と比較して1.46（95% CI：1.29-1.66），一方心血管疾患死のハザード比は1.39（95% CI：1.11-1.73）と，いずれも有意に上昇していた。このように精神疾患と糖尿病が併存すると死亡の危険が高まる。

さて，SMI患者において心血管疾患罹患とそれによる死亡の危険度が高いことは広く認知されるところであるにも関わらず，SMI患者が身体科を受診し心血管疾患危険因子のスクリーニングをしたり治療を受ける割合は低値にとどまっている[22)-24)]。また，SMI患者のなかでも第二世代抗精

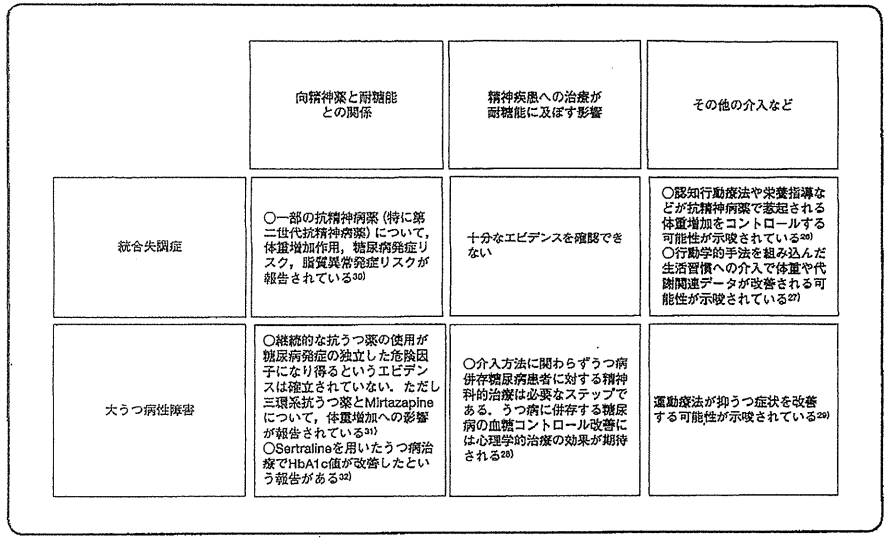

図5．精神科治療と糖尿病

神病薬を服用している患者については，2004年に米国糖尿病学会と米国精神医学会などの関連学会から代謝指標の評価を定期的に実施するよう指針が出されているが，米国のMedicaidを利用している第二世代抗精神病薬服用中の患者において，血糖値や脂質といった代謝指標が検査された頻度は，2005年末までの調査で，指針が発表された後にもほとんど変化していなかったことが報告されている[25]。SMI患者で心血管疾患死の危険度が高いのは，単に危険因子を保有している割合が高いというだけではなく，一次，二次予防に必要な医療が適切に提供されていないことも大きく関わっている。

Ⅳ．精神疾患に併存する糖尿病の治療

最後に精神疾患に併存する糖尿病や肥満の，より良い管理目標達成のための介入方法を検討した研究結果について言及する（図5）。

統合失調症では，抗精神病薬によって惹起される体重増加のコントロールを目的とした非薬物療法の効果を検討したメタ解析が報告されている。これによると，認知行動療法や栄養指導といった非薬物療法による介入は通常の治療法と比較して，慢性期の統合失調症患者においても有意に体重管理の成功と相関したということである[26]。同論文中では，体重管理プログラムに対する患者のアドヒアランスが体重減少と相関しているので，介入方法は患者が治療契約を結びやすいものが選択されることが望ましいとしている。

SMI患者を対象に，生活習慣の改善を目的とした介入の効果を検討した系統的レビューでは，解析対象となった23報中，ほとんどの論文が介入方法に問題解決法やセルフ・モニタリングといった行動学的な手法を組み込んで使用し，このうち12報で体重減少やHbAlc，中性脂肪，血圧などの代謝関連データの改善が認められたと報告している[27]。

一方うつ病併存糖尿病患者に対しては，精神科的治療が精神症状の改善に加えて血糖コントロールの改善にも寄与し得るかどうかについて検討したランダム化比較試験のメタ解析が報告されている[28]。介入方法は大別して①抗うつ薬治療，②心理学的治療（多くの研究で糖尿病療養指導も含めて実施），③Collaborative Care（薬物療法と心理学的治療の併用療法）の3カテゴリーに分類されている。この論文では，介入方法に関わらず，うつ病併存糖尿病患者に対する精神科的治療は必要なステップであり，なかでも血糖コントロールの改善には心理学的治療の効果が期待されると結論付けている。うつ病の治療法とは独立に，抑うつ症状の改善が血糖コントロールの改善と相関するというデータもあることから，うつ病併存糖尿病患者が精神科において適切かつ十分なうつ病の治療を受けることは，精神症状の改善と血糖コントロールの両方を達成する上で基本的な事項であると考えられる。

さらに最近は運動療法が抑うつ症状を改善する可能性があり，その効果は抗うつ薬を用いた薬物療法に劣らないとする報告も出されている[29]。この報告が今後，大うつ病性障害に併存する糖尿病治療にどのような可能性を与えてくれるのか，非常に関心がもたれるところである。

おわりに

精神疾患と糖尿病の関係についてのエビデンスはいまだ十分に確立しているとはいえず，今後さらに研究が進められること，特にわが国における研究が進むことが期待される。

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特集／日常診療に役立つうつ病の知識

身体疾患と合併したうつ病の治療

心　筋　梗　塞

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はじめに

循環器領域において，精神神経因子の異常が病態・予後に影響を与えることは，数多くの研究により明らかである。また関連する学会である日本循環器心身医学会が40年近くの歴史を有しているように，本邦においても循環器疾患診療における精神神経因子異常の重要性は理解されてきた。しかし研究目的の調査は行われるものの，系統的介入を行っている施設はほとんどないのが実情である。

近年この分野において，新たな展開があった。一つはうつが厚生労働省が指定する5大疾病の一つに指定されたことと，もう一つは2009年にAmerican heart associationより冠動脈疾患患者におけるうつの取り扱いに関する詳細なstatement[1]が発表されたことである。これらにより改めて循環器領域におけるうつへの積極的な介入が意識されるようになった。

我々に与えられたテーマは，このような背景のもとで提起されたものである。本稿では，心筋梗塞に合併するうつについて，我々の取り組みを交えながら，最新の知見について解説したい。

Ⅰ．疫　学

まず心筋梗塞に合併するうつの疫学について述べる。心筋梗塞では，うつが発症前と発症後の両者において関連する。うつと診断された患者では冠動脈疾患の発症率が有意に高く，そして心筋梗塞患者ではうつが高頻度に見られる。しかし実際に心筋梗塞患者が発症前にうつと診断されていた，あるいは大うつ病の症状を自覚していた症例は多くない。我々のデータでは，心筋梗塞後2週間から2ヵ月にかけてうつのスコア（PHQ9）に明らかな改善があり，発症前より存在したうつの器質とは別に，心筋梗塞という強い精神的ストレスの影響を考える必要がある。それぞれの関連は強くないが，うつは冠動脈疾患の危険因子であり，一次予防・二次予防のそれぞれの場面において対応すべき重要な病態と考えるべきである。

冠動脈疾患にうつを合併した場合の予後[2]に関する報告は多く，John C. Barefootらはうつが冠動脈疾患の心死亡率を長期にわたって増加させることを示している。また，我々の教室の中村らによると心血管疾患にみられる不安感・怒りも，予後に影響を与えていた[3]。このように心筋梗塞後の精神神経因子異常の予後への影響は大きく捉える必要があることも理解しておきたい。

Ⅱ．機　序

うつが，如何なる機序を介して病態に影響をおよぼすかを考えたい。様々な経路を経る可能性があるが，精神神経因子異常から冠動脈疾患発症に至る経路は，ストレス要因が直接冠動脈硬化に及ぼす影響と，生活習慣病の悪化を介して及ぼす間接的な影響の二つに分けられる[4]（図1）。

直接的な影響として，1）ACTH・血中コルチゾルおよびカテコラミン分泌増加，2）炎症性サイトカイン増加，3）血小板凝集能亢進，4）酸化ストレス増大，5）内皮機能障害，6）自律神経障害を介したものが挙げられている。しかし，これらの因子の何れが最も強く病態に影響を与えるのかは不明である。

うつが間接的に心疾患の病態に影響をおよぼすことも注意すべきである。うつによる生活習慣の変化が肥満・喫煙・食塩摂取・脂質過量摂取につながり，さらには服薬を遵守できない[5]（図2），心臓リハビリテーションなどの運動習慣を保てないなどの機序の報告がある。このように，心筋梗塞後のうつは様々な機序を介して病態に悪影響を与える可能性が有る。うつは多くの危険因子と関連し合いながら予後に影響すると考えられ，このことが介入試験においてうつが独立した危険因子として抽出されないことの一因であると推察される。我々の研究では，心筋梗塞後のうつは，例え軽症で大うつ病でなくても，自律神経機能などに影響を与えており，予後に影響を与え得る可能性がある[6]（図3）。

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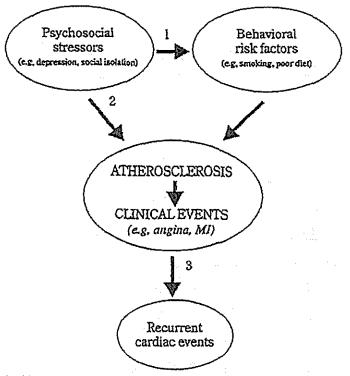
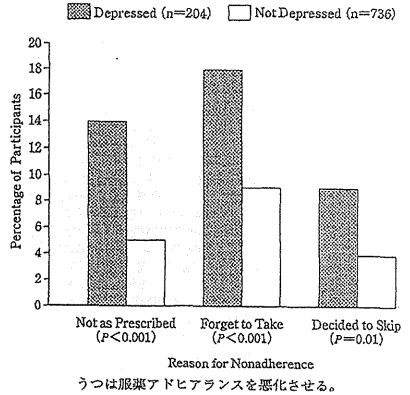


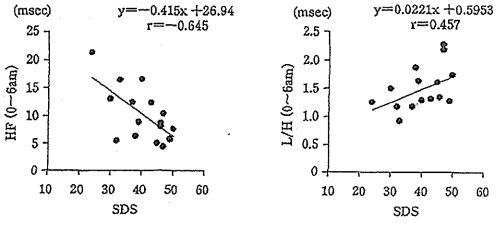
1）精神的ストレスが生活習慣病に及ぼす間接的な影響。
2）精神的ストレスが直接冠動脈硬化の伸展に影響。
3）ストレス・生活習慣病の両者が心事故再発に影響。

図1　精神神経因子異常から冠動脈疾患発症に至る経路（文献4）



うつは服薬アドヒアランスを悪化させる。

図2　外来冠動脈疾患患者におけるうつと服薬アドヒアランスの関係（文献5）



梗塞後うつはほとんどが軽症であるが，自律神経障害（HF，副交感神経指標；L/H，交感神経指標）と関連。

図3　心筋梗塞後抑うつと自律神経障害（文献6）

Ⅲ．循環器医によるうつの評価

心筋梗塞後のうつに対し，循環器科が行うべきスクリーニング検査について述べる。患者が明らかなうつ症状を訴えてはじめて精神神経科に依頼することは，十分な対応とは言い難い。梗塞後うつに対するスクリーニング法について定まったものはないが，前述した2008年のAHAのstatementに示されているフローチャートが一つの基準となる[1]（図4）。AHAではスクリー

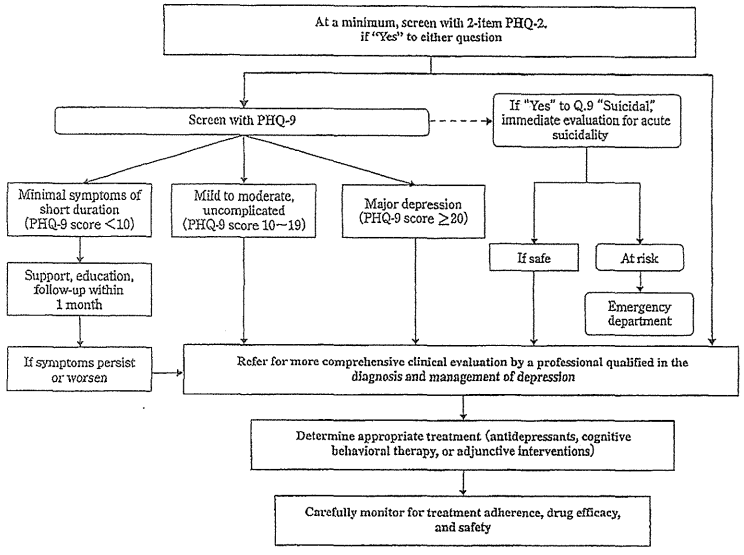


図　4　冠動脈疾患に対するうつのスクリーニング（文献1）

ニングとしてPHQ（Patient Health Questionnaire）2とPHQ9を用いたものを推奨している。第一段階としてPHQ2を用い「何事にもほとんど興味がわかない，または楽しめない」「気分が落ち込む，憂うつになる，または絶望的な気持ちになる」という大うつ病の徴候の有無を判定する。そしてPHQ2が陽性の場合にPHQ9によるさらに詳しい評価を行う，2段階のスクリーニング法が提案されている。このように，PHQを用いた自己記入式質問紙試験を用いて，うつを抽出し，その結果に基づき精神神経科専門医へ診療を依頼する流れが推奨されており，その妥当性も検証されている[7]。

我々も，このフローチャートに忠実に沿うことを目指していたが，実際の医療現場にそのまま適合するのは難しい。本邦の医療事情として，精神神経科がない病院の循環器科であったり，精神神経科医師の絶対数が少なく十分な連携が難しい病院であったり，なにより患者が精神神経科受診に強い抵抗感を感じることがあるなど障害は少なくない。

我々は，AHAのフローチャートを，当院で実施可能な形へ修正し実施している（図5）。大きな修正部分は，PHQを最初からPHQ9を用い一段階のシンプルな形とすること，精神神経科への依頼に十分なフィルターをかけることである。当院にはリエゾンナースがおり，このシステムの中で大きな役割を果たしている。各施設で状況が異なるので，AHAのstatementの運用には実情に沿った修正が必要と考えている。

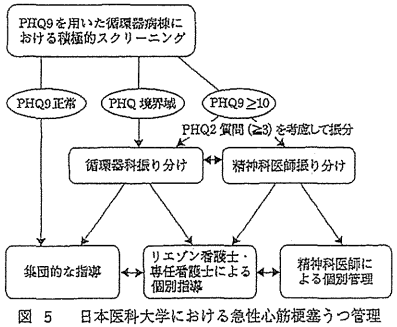


図　5　日本医科大学における急性心筋梗塞うつ管理

循環器科においてうつをスクリーニングする場合の注意点として，1）PHQなどが簡易検査である限界を理解すること，2）自殺念慮などが含まれる患者情報であるので，結果を臨床に反映させる絶対的な義務が生じること，3）データを活かすには相応の態勢（システム構築）が必要であること，4）ICD植込み症例のような重症例にはスクリーニングは馴染まず別途対応すべきこと，が挙げられる。

Ⅳ．治　　療

治療は，原則として精神神経科医師に判断をあおぐことが望ましい。特に大うつ病と判断される場合は，精神神経科医師に任せるべきと考える。精神神経科医師との連携が難しく循環器科において管理をしなければならない場合には，精神神経科医師による治療の質の管理が必要と思う。もちろん，自殺念慮の訴えがある場合は，至急で精神神経科医師受診となることは言うまでもない。

具体的な治療法として，AHAのガイドラインによると，薬物療法と認知行動療法が挙げられている。両者は同等の治療効果を有するとされているが，詳しくは，他稿にお任せをしたい。

我々の経験では，発症後2週間の心筋梗塞後症例の約15％でPHQ9異常あり（10以上）と判定されたが，大多数は軽症であった。また，退院後2ヵ月にかけて，およそ半数の症例でPHQ9が正常化している。このように，うつのスクリーニング検査陽性であっても，直ちに精神神経科受診につながらず経過観察で良い症例が少なくない。我々は，このような経過観察可能と判断された症例に対し，ストレス管理に関する集団指導と，希望がある場合はリエゾンナースによる個別の面談を行っている。

最　　後　　に

本稿では，心筋梗塞に合併するうつを概説した。近年になり社会の要請（国民病5大疾病）としてうつに対する介入が求められている。これはQOLの改善も，社会へのスムーズな復帰のために必要であることを示している。また，うつは冠動脈疾患の強力な予後規定因子であり，様々な機序を介して心筋梗塞後の病態に影響を与えることも明らかである。うつに対する介入が独立し予後を改善するとした大規模研究はないが，冠危険因子と相互に影響し合う因子として介入することにより予後の改善を期待できることは間違いがない。

心筋梗塞後患者に対する，うつのスクリーニングと系統的な介入システムの確立は，危険因子の包括的管理の軸として役立つものである。本邦の実情にあった梗塞後のうつ管理法は未だ確立されていないが，まずは，導入可能な形で始めるべきと思う。近年の循環器医療の高度化にともない，患者へ強い精神的ストレスがかかるようになっている。本稿がきっかけとなり，心筋梗塞後うつの重要性を理解していただきたい。AHAのstatementで用いられているPHQの質問表は，インターネット上に掲載されており，利用可能であることを最後の言葉としたい。

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シンポジウム：睡眠医学が心身医学に寄与できること

循環器内科における睡眠障害とうつ病に関する観察研究

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抄録：本研究では循環器疾患患者の気分状態，睡眠時無呼吸症候群（SAS）を含む睡眠障害，眠気，QOL，心機能などを多角的に評価した．今回，中等度以上のうつ症状を認めたのは5.7%と少数であったが，うつ症状の程度は不眠やQOLとともに右心系への後負荷とも関連性が認められた．一方，中等症以上（AHI≧15）のSASの罹患予測率は58.5%と高率で，その重症度は気分状態や眠気などと関連性がなく無症候性であったが，左房径，左室駆出率，E/eʼなど左心系の心機能とは関連性を有した．うつ病とSASは双方とも心機能に影響を与えるために積極的なスクリーニングを要すると考えられたが，中等症以上のうつは「PHQ-2のどちらかの陽性」，中等症以上のSASはパルスオキシメータで「3%ODI>7.5」というきわめて簡易なツールでいずれも95%前後の感度で抽出が可能であった．また循環器医による「うつ」の見立てによる抽出率は，うつ病の存在を意識しながら問診をするだけでも飛躍的に向上することが示された．

Key words：循環器疾患，睡眠時無呼吸症候群，うつ，睡眠障害，眠気

はじめに

近年，中高年の自殺は大きな社会問題となっており，その背景にあるうつ病・うつ状態がプライマリ・ケアにおいて早期に診断されることの重要性が指摘されている．うつ病は循環器疾患とも密接な関係がある．循環器疾患を有する患者の中でうつ病を併発する割合は高く[1]，うつ病を併発すると一般に予後不良で死亡のリスクが高くなる[2)3)]だけではなく，生活の質が下がり[4]，また医療費が多くかかる[5)6)]といった報告もある．米国心臓病学会（American Heart Association：AHA）は，うつ病が心血管罹患率および死亡率の増加と関連するため，スクリーニングテストによるうつ病の早期発見，早期治療に関する勧告をヘルスケア医療提供者に行っている[7]．

うつ病と循環器疾患の双方に多くみられる病態として睡眠障害がある．うつ病において不眠は必発であり，循環器疾患では不眠のみならず睡眠時無呼吸症候群（sleep apnea syndrome：SAS）との関連も深い．不眠は糖尿病や高血圧症などの生活習慣病の誘因となるし[8)~10)]，肥満は循環器疾患と睡眠時無呼吸症に共通するリスク・ファクターである．また，特にわが国では国民の平均睡眠時間が減少しつづけているが，さらに循環器疾患患者の睡眠時間は健常人に比して短いことが指摘されている[12)]．

これまで，うつ病やSASを含めた睡眠障害が循環器疾患患者にどの程度存在するのかをそれぞれに論じた研究はあったが，それらを総括的に観察した研究はみられない．本研究の目的は，まずうつ病と睡眠呼吸障害（sleep disordered breathing：SDB）を含む睡眠障害の有病率と重症度の現状を明らかにし，これらが相互に及ぼし合う影響やQOLとの関連性を検討することである．加えて，循環器内科医がうつ病やSDBの合併を，より簡便により確実に抽出しうる方法論を提案することが本研究の重要な目的である．

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方法

1．対象（Table 1）

対象は，2010年5月10日～2012年10月31日に久留米大学心臓・血管内科病棟に入院した循環器系疾患患者で循環器科担当医が対象基準を満たすと判断した患者のうち，適格基準および除外基準を満たし，研究計画についての詳細な説明の後，同意が得られた患者とした．適格基準と除外基準は以下のとおりである．

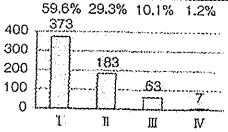
適格基準

1）20歳以上80歳以下で循環器基礎疾患を有する患者
2）性別不問
3）本研究の参加について文章で本人の同意が得られた者

また以下を除外基準とし，いずれかの項目に抵触する患者は組み入れないこととした．

1）認知症および明らかな知的障害のある患者
2）ショック状態を呈している患者
3）意識障害を有する患者
4）人工呼吸器装着中の患者
5）その他，主治医が不適当と判断した患者

Table 1　適格基準と除外基準，および対象者の背景

全体（n=628）	
年齢	63.0±12.3
性（男性）（%）	442名（70.4%）
BMI	24.0±4.1 （25を超える肥満は35.7%）
収縮期血圧　mmHg	125.4±20.3
拡張期血圧　mmHg	73.4±12.8
心拍数/min	71.5±14.5
LVEF %	60.3±14.7
血中クレアチニン値	1.65±3.0
NYHA class	59.6% 29.3% 10.1% 1.2% 
有病率	
高血圧	387/626（61.8%）
虚血性心疾患	351/626（56.1%）
糖尿病	238/626（38.0%）
不整脈	174/626（27.8%）

適格基準：①20歳以上80歳以下，②性別不問，③本人の同意が得られた者
除外基準：①認知症および明らかな知的障害のある患者，②ショック状態を呈している患者，③意識障害を有する患者，④人工呼吸器装着中の患者，⑤その他，主治医が不適当と判断した患者

2．評価項目（Fig. 1）

1）循環器内科担当医および看護スタッフが以下の項目を評価

1）基礎心疾患：虚血性心疾患，心筋症，弁膜症，うっ血性心不全，不整脈，高血圧症，先天性疾患，心膜心筋炎，大動脈疾患，末梢血管，肺高血圧，感染性心内膜炎，心臓腫瘍，代謝性疾患，その他
2）合併症の有無：高血圧，糖尿病，脂質異常症，脳卒中，慢性肝疾患，慢性呼吸不全，癌
3）身体所見：身長，体重，腹囲，血圧，脈拍数
4）検査所見：心電図，心エコー検査，弁膜症の有無，NT-proBNP値，血清クレアチニン値
5）循環器疾患の重症度分類：NYHA（New

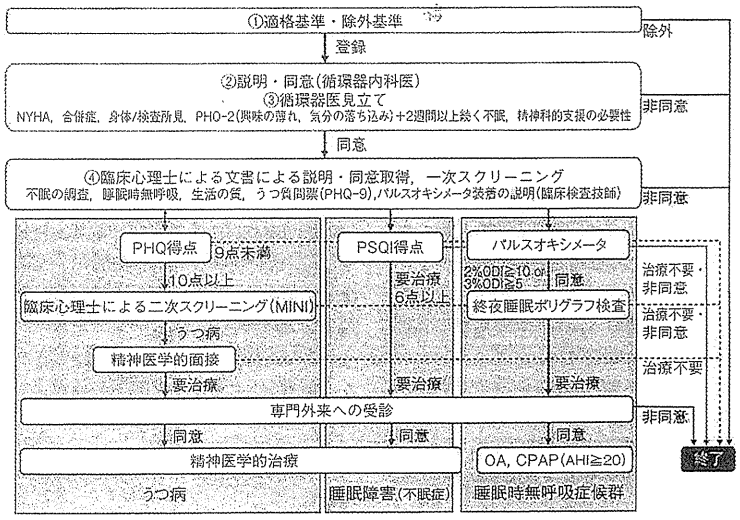


Fig. 1 久留米大学病院における循環器内科入院患者に対するうつ病，睡眠障害，睡眠時無呼吸症候群の評価

York Heart Association）心機能分類

6）循環器科内科医が通常の問診後にうつ状態に関する見立て

ⅰ．興味や楽しみの薄れ

ⅱ．気分の落ち込みや憂うつ感

ⅲ．2週間以上続く不眠

7）循環器内科看護スタッフによる情報収集

精神科既往歴，家族歴，治療歴，喫煙状況，飲酒状況

2）一次スクリーニング

臨床心理士が一次スクリーニングとして自記式評価尺度を対面方式で実施．

1）うつ状態（Patient Health Questionnaire：PHQ-9）＋2週間以上続く不眠

2）睡眠評価尺度（Pittsburgh Sleep Quality Index：PSQI）

3）SAS（習慣的いびきの有無，呼吸停止の有無，Epworth Sleepiness Scale〔ESS〕）

4）生活の質（QOL）評価尺度（日本語版 EQ-5D）

またSASのスクリーニングとしてパルスオキシメータによる一晩の睡眠中の酸素飽和度の測定を行い，2%および3%ODIを算出．

一次スクリーニングの結果，PHQ-9で10点以上の中等症以上のうつ病疑いの患者，およびPSQIで5.5点以上の睡眠障害疑いの患者には結果を書面でフィードバックし，精査を希望した者は専門外来に紹介した．

3）SASの二次スクリーニング

2%ODI>10，あるいは3%ODI>5のSDB疑いの患者のうち同意が得られた者に対しては，終夜睡眠ポリグラフ検査（PSG）を行った．

4）倫理的事項

a）倫理的問題点

本研究は循環器疾患と精神疾患に関する簡単な質問形式で行うため，患者の身体的負担は少ないと考えられるが，精神的苦痛を与えないよう，調査は身体的状態が落ち着いているときに行うこととした．

b）患者の保護

本治療研究は，「医療・介護関係事業者における個人情報の適切な取扱いのためのガイドライン」，およびヘルシンキ宣言（英国エジンバラ修正2000年，ワシントン注釈追加2002年，および東京注釈追加2004年）の基本理念を遵守して行われた．患者情報の漏洩防止策として，施設番号と症例登録用紙の番号を組み合わせたものを匿名化番号（研究登録番号）として個人の匿名化を行った．回収した氏名などの個人情報が特定されない調査票は，鍵のかかる書類ケースに保管され，解析用データベース作成時にはネットワークに接続されていないパソコンを利用した．また匿名化番号による情報管理を行い，個人名などの個人を特定する情報はデータベースに入力せず，データベース完成時には調査票はシュレッダー処理して破棄した．

c）同意の取得

本治療研究の開始に先立ち，臨床心理士および循環器科担当医は説明同意書を用い，①本研究の概要，②意義・目的，③方法，④参加について，十分な説明を行った．また患者に対して質問する機会と試験に参加するか否かを判断するのに十分な時間を与えた．患者が本試験の内容を十分に理解したことを確認した後，患者本人の自由意思による研究参加の同意を文書により取得した．同意文書は1部複製して患者本人に手渡し，原本はカルテに保管した．

なお，本研究は久留米大学倫理委員会の承認を得た．

結果

1．対象者の背景（Table 1）

2010年5月1日～2012年10月31日に久留米大学病院心臓・血管内科病棟に入院した患者のうち，本研究の参加に同意が得られたのは628名であった．

患者背景を**Table 1**に示した．628名（男性442名，女性186名）の平均年齢は63.0±12.3歳，BMIは24.0±4.1であった．検査所見は血圧125.4±20.3/73.4±12.8 mmHg，心拍数71.5±14.5，左室駆出率（LVEF）は60.3±14.7%であった．NYHA分類はⅠ度59.6%，Ⅱ度29.3%，Ⅲ度10.1%，Ⅳ度1.2%で，Ⅰ～Ⅱ度の軽度の患者が中心であった．主な合併症の有病率は高血圧61.8%，虚血性疾患56.1%，糖尿病38.0%，不整脈27.8%であった．

2．PHQ-9によるうつ病自記式検査の結果（Fig. 2）

Fig. 2の左下にうつ病尺度であるPHQ-9の得点分布を示した．軽度（5～9点）が20.3%，大うつ病を88%の特異度で抽出できる10点以上は5.7%であった．

PHQ-9による「中等度以上のうつ」と「軽度以上のうつ」の診断能について，AHAが推奨している，「興味や楽しみの薄れ」と「気分の落ち込みや憂うつ感」によるPHQ-2（2項目のいずれかが「あり」ならば陽性と定義），またそれに「2週間以上続く不眠」の項目を加えた3項目（PHQ-3）で評価した場合の感度と特異度を**Fig. 2**の右側に示した．中等度以上のうつの抽出に対するPHQ-2の感度は94.4%，特異度は67.2%で，軽度以上のうつの抽出に対するPHQ-2の感度は77.3%，特異度は78.0%であった．一方，中等度以上のうつの抽出に対するPHQ-3の感度は100%，特異度は40.9%で，軽度以上のうつの抽出に対するPHQ-3の感度は97.5%，特異度は51.3%であった．

さらに循環器科内科医が通常の問診によりうつがどの程度正確に抽出できたかを，循環器医に対するうつ病のレクチャー（2012年5月27日）の前と後に分けて感度と特異度を算出し，検討した．するとレクチャー前の中等度以上のうつ症状の抽出は感度が29.2%・特異度は90.8%であったが，レクチャー施行後は感度が90.0%に大幅に改善し，一方で特異度は66.1%

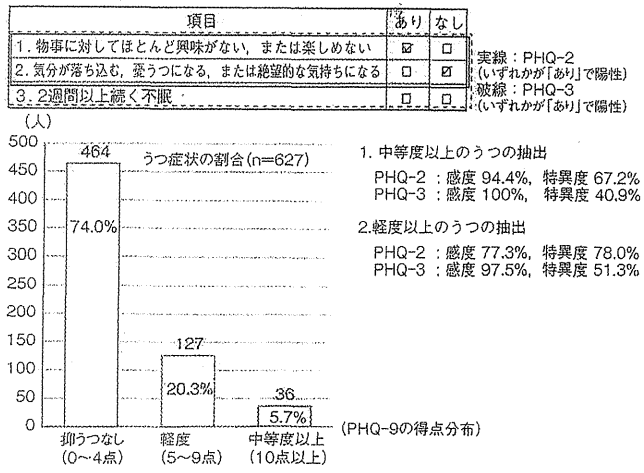


Fig. 2　うつ症状の割合と PHQ-2，PHQ-3 による抽出

Table 2　軽度以上のうつ病群（n=163）と非うつ群（n=464）との比較

	非うつ群	軽度以上のうつ病群	Wilcoxon		非うつ群	軽度以上のうつ病群	Wilcoxon
年齢	64.1±11.5	59.8±14.2	▼ 0.0029	下大静脈吸気時	7.9±3.9	8.6±4.4	0.1122
体重	62.9±12.5	61.2±15.9	▼ 0.0091	下大静脈呼気時	14.5±4.4	15±5.3	0.6491
身長	161±8.8	160.6±9	0.5154	呼吸・変化率	46.5±15.3	44.1±15.6▼	0.0306
BMI	24.1±3.8	23.5±4.9	▼ 0.0036	心室中隔 E/A	25.3±14.3	28.3±14.9▲	0.0123
腹囲	87.2±10.6	85.3±14.09	▼ 0.0159	推定収縮期肺動脈圧	35.2±16.1	38.9±17.3▲	0.0241
PSG AHI	24.4±18.7	25.9±31.3	0.279	E	77.3±33.2	77.2±27.5	0.4421
3%ODI	12.1±9.9	12.9±13.9	0.2468	A	75.8±25.6	69.1±24.0▼	0.0083
身長	161±8.8	160.6±9	0.5154	E/A	1.1±0.7	1.2±0.7 ▲	0.0104
NT-proBNP 値*	786.8±1733	1128.6±2126	0.1379	Dct (ms)150 未満	222.5±87.2	200±66.9▼	0.0023
クレアチニン重症度	1.5±2.6	1.5±2.0	0.2671	E/é	15.2±9.7	15±8.6	0.9424
PSQI	4.9±3.0	7.9±3.8	▲<0.0001	左室駆出率	61.1±13.7	57.7±17.1	0.0712
ESS	4.6±3.4	6.4±4.2	▲<0.0001	Simpson	48.5±15.0	39.6±16.9▼	0.0022
EQ-5D	0.9±0.2	0.7±0.3	▼<0.0001	左房径	39.2±8.3	39.5±8.7	0.5644

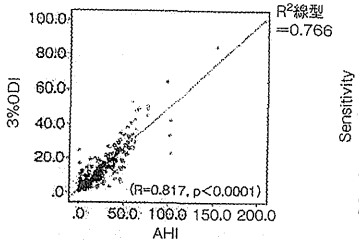
▼significantly lower in depressive patients　▲significantly higher in depressive patients
*'NT-proBNP' 値の検討では，eGFR 値を算出し，CKD の Stage 分類でIV期とV期の腎不全群は除外した．

に低下した．

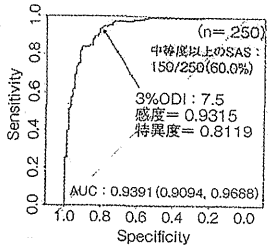
3．軽度以上のうつ病群と非うつ病群の各所見の比較（Table 2）

軽度以上のうつ病群（163 名，以下うつ病群）と非うつ病群（464 名）の各所見を Table 2 に示した．年齢はうつ病群で有意に若く（59.8±14 vs. 64.1±12），体重，BMI，腹囲はうつ病群で低かった．自記式検査の結果では，不眠を示す PSQI 得点（7.9±4 vs. 4.9±3）と眠気を示す ESS 得点（6.4±4 vs. 4.6±3）がともにうつ病群で有意に高く，QOL 得点（0.7±0.3 vs. 0.9±0.2）はうつ病群で有意に低かった．心エコー所見の比較では，右室-右房の圧較差（28.3±15 vs. 25.3±14）や推定収縮期肺動脈圧（38.9±17 vs. 35.2±16）が有意にうつ病群で高かった．

3%ODI 閾値	特異度	95%信頼区間		感度	95%信頼区間	
	推定値	下限	上限	推定値	下限	上限
5	0.5149	0.4158	0.6139	0.9932	0.9795	1
7.5	0.8119	0.7327	0.8812	0.9315	0.8836	0.9658
9	0.8515	0.7822	0.9208	0.8493	0.7945	0.9041
9.95	0.9109	0.8515	0.9604	0.8356	0.774	0.8973



3-1：3%ODI と AHI 値の相関



3-2：AHI≧15 を陽性と定義した際の ROC 解析

Fig. 3　パルスオキシメータによる中等度以上の SAS の抽出

また拡張後期の心房収縮による A 波はうつ病群で低く（69.1±24 vs. 75.8±26），deceleration time（200±67 vs. 222.5±87）と Simpson 法による左室心拍出量（38.9±17 vs. 48.5±15）はうつ病群で有意に低かった．

4．3%ODI カットオフ値の検討（Fig. 3, 4）

フル PSG を施行した 250 例において中等度以上（無呼吸低呼吸指数：AHI≧15）の SAS を認めたのは 60.0%（150/250）に上った．この中等度以上の SAS 群のパルスオキシメータによる診断能を ROC 曲線を用いて算出し，Fig. 3 の右側に示した（Fig. 3-2）．ROC 曲線を用いて算出した 3%ODI の最良のカットオフ値は 7.5 で，このカットオフ値を用いれば中等度以上の SAS 群を感度 93.2%，特異度 81.2%という高い水準で抽出が可能であった．3%ODI のカットオフ値を 7.5 として，全 626 名中の SAS の推定有病率を算出し，Fig. 4 に性別，肥満の有無別にグラフでその割合を示した．その結果，全体の 58.5%に中等度以上の SAS の罹患が予測された．推定罹患率は男性で 61.7%，女性 50.4%，

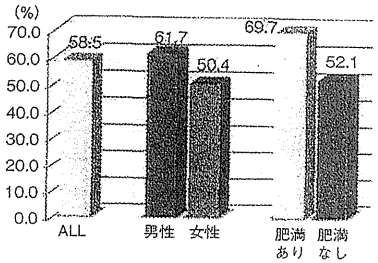


Fig. 4　3%ODI 値のカットオフ値を 7.5 とした場合の SAS（AHI≧15）の推定有病率（n=626）

肥満群で 69.7%であったが非肥満群でも 52.1%と高率であった．

5．3%ODI と各自記式検査の相関関係（Table 3）

3%ODI 値および各自記式検査の相関係数（上段）と確率（下段）を Table 3 に示した．最も関係性が高かったのはうつと不眠（r=0.48, p<0.0001）であった．

QOL は，EuroQoL（EQ-5D）にて評価した．

Table 3　3%ODI 値および各自記式調査の相関関係

	3%ODI	PHQ-9	PSQI	ESS	EQ-5D
3%ODI		0.0931 0.0474	−0.05316 0.2583	0.01734 0.7126	−0.01734 0.7126
PHQ-9	0.0931 0.0474		0.47512 <.0001	0.24087 <.0001	−0.35564 <0.0001
PSQI	0.05316 0.2583	0.47512 <.0001		0.09449 0.0179	−0.24964 <0.0001
ESS	0.01734 0.7126	0.24087 <0.0001	0.09449 0.0179		−0.02941 0.4623
EQ-5D	−0.01734 0.7126	−0.35564 <.0001	−0.24964 <.0001	−0.02941 0.4623	

n＝627
上から順に，Spearman 相関係数，検定 p 値（仮説は r＝0）を表す

Table 4　心機能評価との相関関係

	NTpro-BNP*	クレアチニン	左室駆出率	左房径	E/é	下大静脈吸気	下大静脈呼気	吸気-呼気変化率	RA-RV PG	推定収縮期肺動脈圧
3%ODI	0.09652 0.0619	0.27781 <.0001	−0.1786 0.0001	0.24607 <.0001	0.19524 0.0005	0.12585 0.0106	0.03234 0.5127	−0.17795 0.0003	−0.04126 0.4832	0.01359 0.8181
PHQ-9	0.00446 0.9198	0.02703 0.5	−0.04249 0.2889	−0.01694 0.6732	−0.02693 0.5776	0.01784 0.672	−0.01349 0.7488	−0.03371 0.4243	0.12938 0.0096	0.08888 0.0769
PSQI	0.06536 0.1401	0.07734 0.0533	−0.05936 0.1382	0.0782 0.0512	0.09994 0.0383	0.00752 0.8584	0.00063 0.988	0.00243 0.954	0.15786 0.0015	0.10651 0.0339
ESS	−0.07966 0.072	0.00627 0.8756	0.08252 0.0392	−0.04933 0.2192	−0.11108 0.0212	−0.0492 0.2426	−0.03827 0.3634	0.04063 0.3355	−0.22977 <.0001	−0.23055 <.0001
EQ-5D	−0.09625 0.0296	−0.09456 0.018	0.0465 0.2457	−0.03384 0.3995	−0.0495 0.3058	0.03246 0.4409	−0.03019 0.4735	−0.05227 0.2151	−0.14463 0.0037	−0.09467 0.0595

n＝625
上から順に，Spearman 相関係数，検定 p 値（仮説は r＝0）を表す
*NT-proBNP 値の検討では，eGFR 値を算出し，CKD の Stage 分類でIV期とV期の腎不全群は除外した

EQ-5D は，1990 年に発表された自己記入回答式の質問紙で，健康状態に関する 5 つの質問（移動の程度，身の回りの管理，普段の生活，痛み・不快感，不安・ふさぎ込み）からなる 3 段階選択式回答法で，死亡を 0，完全な健康を 1 として，回答の組み合わせにより 245 通りの健康状態に効用値が割り当てられた包括的尺度である．QOL と相関が高かった項目はうつ（r＝−0.36, p<0.0001）で，次いで不眠（r＝0.25, p<0.0001）が QOL と関連していた．

一方，SDB の診断において重要な指標となる 3%ODI は，うつや不眠などいずれの項目とも相関を認めず，眠気とも関連性がなかった．眠気が唯一弱いながら相関を示したのはうつ（r＝0.24, p<0.0001）であった．

6．エコー所見の関連性について（Table 4）

PHQ-9（うつ），PSQI（不眠），ESS（眠気），3%ODI 値（SAS）と心エコー所見との関連性に関して，相関係数（上段）と確率（下段）を Table 4 に示した．うつや不眠，眠気などいずれの自記式評価とも相関を認めなかった 3%ODI 値は左房径（r−0.25, p<0.0001），E/é 値（r＝0.20, p＝0.0005）など左心系の機能と弱いながら相関が認められた．また吸気時と呼気時の下大静脈径の変化率とも弱い逆相関（r＝−0.18, p＝0.0003）を示した．うつ・不眠・QOL は，これらの左心系の機能とは関連性を認めず，一方で右室-右房の圧較差（PHQ-9：r＝0.13, p＝0.01, PSQI：r＝0.16, p＝0.002, EQ-5D：r＝−0.14, p＝0.004）や推定収縮期肺動脈圧（PSQI：r＝0.11, p＝0.03）と弱い相関を認めた．

また，眠気は右室-右房の圧較差（r＝−0.23, p<0.0001）や推定収縮期肺動脈圧（r＝−0.23, p<0.0001）の双方と負の相関が認められた．

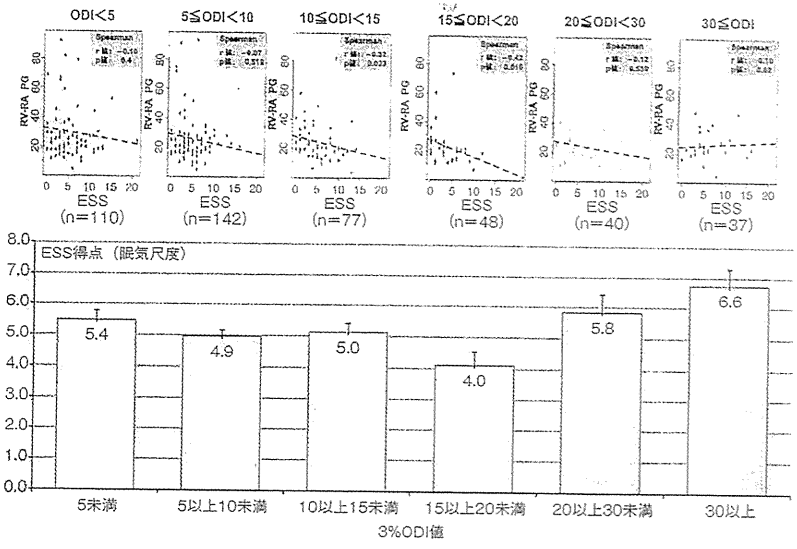


Fig. 5　ESS と右室-右房圧較差の相関（3%ODI 別）（n＝454）

7．SDB の重症度と眠気，右室-右房の圧較差の関係性について（Fig. 5）

3%ODI の重症度別の ESS 得点を，Fig. 5 の下段に示した．眠気は 3%ODI が 20 未満までは SDB の重症度とは関連を認めず，特に中等症以上の SAS がほぼ確実である 15≦3%ODI<20 の群（n＝48）で ESS 得点は最も低かった（平均 4.0 点）．また最も重症度の高い 30≦3%ODI 群（n＝37）でも ESS の平均値は 6.6 点（カットオフ 10 点）に留まった．

眠気は右室-右房の圧較差や推定収縮期肺動脈圧の双方と負の相関を認めたため，3%ODI の重症度別に右室-右房の圧較差と ESS 得点の相関関係を検討し，Fig. 5 の上段にその分布表と相関係数（上段）と確率（下段）を示した．その結果，両者の負の相関は 10≦3%ODI<15（r＝−0.32, p＝0.02）で有意となり，15≦3%ODI<20（r＝−0.42, p＝0.02）で最大となり，3%ODI が 20 を超えると再び相関関係は消失した．

考察

今回の調査では，中等度以上のうつの有病率は 5.7%と，これまでの報告[11]（27 編のメタ解析で 22%）よりも低かった．これは，約 90%が NYHA II 度以下の軽度の心不全患者が対象であったこと，カウンセラーとの対面方式という構造化面接に近い手法で自記式検査を施行したことが影響したと思われた．

しかし，それでもQOL尺度と比較的強い相関があったことは注目すべきで，心不全が軽度でも，QOLの改善には「うつ」に対するケアが重要であることが示唆された．

中等度以上のうつ症状の抽出に関しては，AHAが推奨するPHQ-2の感度は94.4%，特異度は67.2%で，改めてその感度の高さが示唆された．軽度以上のうつ症状の抽出に関しても，感度は77.3%，特異度は78.0%とPHQ-2はバランスの良い抽出法であった．今回は，それに「2週間以上続く不眠」の項目を加えたPHQ-3によるうつ症状の抽出を試みたが，感度は中等度以上で100.0%，軽度で97.5%と上がるものの，特異度はそれぞれ40.9%，51.3%と低く，偽陽性が多いため実用性は低いと思われた．

さらに循環器科内科医がどの程度うつを抽出できているかを検討するために，入院時に日頃行っている循環器的面接を行った後に「うつの精神的支援の必要性の有無」を評価したところ，見立てによるうつの抽出の感度は29.2%と低率に留まった．そのため，循環器医師によるうつの診断能の向上を目的として，2012年5月17日に循環器医に対して①うつの基本的事項，②AHAの勧告とうつ病の抽出と治療の重要性，③質問の仕方，について約1時間程度のレクチャーを行い，うつ病の抽出を意識しながら問診を行ったうえで同様の評価を行ったところ，感度は90.0%に大幅に改善した．これは，精神医療が専門の医療従事者でなくても，うつの基本的事項を理解し，うつの存在を意識した面接を行えばうつ病患者を抽出することが可能であることを端的に示す結果と考えられる．一方で特異度が66.1%に低下し，偽陰性率は9.2%から33.9%に上昇した．今後はより的確にうつ病群を抽出していくことが課題に挙げられた．

PHQ-9スコアと各項目との相関の検討では，不眠が最も関連性が高く，不眠のケアが循環器患者におけるうつ病治療においても重要であることが示唆された．

一方，バルスオキシメータ検査とフルPSGを併せて行った250名のデータを解析し，バルスオキシメータ検査によるAHI≧15群の診断能を検討したところ，3%ODIのカットオフ値は7.5が，最もバランスの良い抽出が可能であった．通常，SDBのスクリーニングは，3%ODI=10をカットオフ値として抽出されることが多いが，循環器疾患患者では7.5前後のより広い範囲で抽出する必要があると考えられた．この理由としては，循環器疾患患者には，やせ型の者（今回の対象は，BMIが25未満の非肥満者が64.3%）や中枢性無呼吸が多いために，無呼吸がSpO_2の低下に反映されにくい可能性が考えられた．この7.5をカットオフ値とすると，中等度以上のSASは58.5%ときわめて高い罹患率が推定された．

3%ODIは，うつや不眠，QOLの尺度とはまったく相関性が認められなかったが，心エコー所見との相関では，うつ・不眠・QOLは，右室-右房の圧較差や推定収縮期肺動脈圧と弱い相関を認め，一方で3%ODI値は左房径，E/é値など左心系の機能と相関するなど，3%ODIとうつや不眠はそれぞれ別のルートで心機能に影響，あるいは心機能障害の影響を受ける可能性があると思われた．これらの結果はうつや不眠，SASは心機能障害の予防という視点に立っても，いずれも治療対象として重要であると思われた．

3%ODIは，うつや不眠，QOLの尺度，さらに眠気の尺度とも関連性を認めなかった．眠気の詳細をみると，中等症以上のSASがほぼ確実である15≦3%ODI<20の群でESS得点は平均4.0点と最も低く，最も重症度の高い30≦3%ODI群でもESSの平均値は6.6点と眠気の指標となる11点を大きく下回った．この結果は循環器疾患患者では睡眠時間が少なく，SASがある場合でも健常人に比べ眠気の自覚が生じにくいとするArztらの報告[12]に沿うものである．SAS患者の大半は眠気の自覚により治療機関を受診する．そのため，眠気の自覚の乏しさは患者自身がその罹患に気づきにくいばかりでなく，治療の必要性の理解にも支障となる可能性がある．

うつ・不眠・QOLは，右室-右房の圧較差や推定収縮期肺動脈圧が高いほど，うつや不眠が強くなり，QOLが下がるという関連性を示したのに対し，眠気は右室-右房の圧較差や推定収縮期肺動脈圧が高いほど眠気は少なくなるという逆向きの相関を認めた．これらの結果は，肺うっ血をはじめとする右心負荷が交感神経を介して眠気の軽減に寄与する可能性を示唆した．3%ODIの重症度別に右室-右房の圧較差とESS得点の相関関係を検討した結果，両者の負の相関は10≦3%ODI<15（r=−0.32，p=0.02）で有意となり，15≦3%ODI<20（r=−0.42，p=0.02）で最大となり，3%ODIが20を超えると再び相関関係は消失した．これらの結果は，特に中等症のSAS患者で右心負荷が眠気の軽減に関連する可能性を示した．

結論

循環器疾患患者において，うつ症状は心機能やQOLに影響するために積極的に治療対象にすべきであると考えられた．循環器医はその重要性と基本的事項を理解し，何よりそれを意識することで抽出率が飛躍的に上がることが示された．

循環器疾患患者において，SASは眠気やうつとは相関しないため見逃されやすい危険性を多分にはらんでいると考えられる．循環器疾患患者の6割に治療が必要である中等症以上のSASが合併することを念頭に置かねばならない．なぜならば，3%ODI値が左房径，E/é値など左心系の機能と相関したように，SASは心機能障害に少なからず関連し，心不全の悪化や心血管イベントの再発に関連する可能性があるためである．このように循環器疾患患者のSASはその「無症候性」が特徴の一つであり，特に自覚がなくても積極的にパルスオキシメータによるスクリーニングが重要である．またこの「無症候性」の原因となる眠気の軽さへの関与が疑われた右室-右房の圧較差や推定収縮期肺動脈圧など右心系負荷の指標については今後検討を重ねる予定である．

本研究により，うつとSASの双方が抽出および治療対象として重要であることが改めて浮き彫りとなった．中等症以上のうつはPHQ-2のどちらかの陽性，中等症以上のSASはパルスオキシメータでの3%ODI>7.5という，きわめて簡易なツールでともに95%前後の感度で機能する点を最後に強調したい．

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Abstract

Relationship between Severity of Sleep Disordered Breathings and Depression, Sleep, Sleepiness and Cardiac Function in Patients with Circulatory Disease

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Background：Studies have suggested that both depression and sleep disordered breathing (SDB) are strongly associated with circulatory disease. However, the relationship between SDB and sleep or depressive symptoms is still uncertain.

Methods：Cross-sectional, analytical and exploratory study. The sample consisted of 628 patients. Data were collected from consecutive adult patients referred to the Department of Cardio-Vascular Medicine, Kurume University School of Medicine Unit from May 2010 to October 2012. All patients routinely completed a comprehensive questionnaires that included question about QOL (EQ-5D), sleep habits (PSQI), subjective sleepiness (Epworth Sleepiness Scale), and depression (Patient Health Questionnaire-9). All patients were screened for SDB using pulse oximeter and were performed echocardiography. Furthermore, of the 628 patients, 250 were performed full polysomnography.

Results：Depression was present in only 5.7% of patients. But the degree of the depression symptoms had associations with insomnia, QOL, sleepiness and the right ventricle afterload. SDB (AHI≧5) was present in 83.5% of patients (10.6% central [CSA], 72.9% obstructive sleep apnea [OSA]). 3%ODI (or AHI) was not correlated with PHQ-9, PSQI, ESS, QOL；left atrial diameter (LAD) and the early mitral annular velocity (E/é) were correlated with SDB severity ($p<0.001$). On the other hand, most of patients (91.2%) with both heart failure and SDB did not complain of sleepiness. Of the 138 patients who meet the clinical criteria for CPAP therapy, 83 patients refused to use CPAP and the rest of 55 patients (39.9%) were prescribed CPAP. The SAS patients refused to use CPAP showed significantly lower scores in ESS, PHQ-9 and obstructive apnea index than patients using CPAP.

Conclusion：This study demonstrates that SDB induces a functional burden on the left atrium, while depression symptoms had association with right ventricle afterload. In the patients with heart failure, the absence of subjective sleepiness may decrease the rate of utilization of CPAP.

Key words：circulatory disease, sleep apnea syndrome, depression, sleep disorder, sleepiness

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Original Article

Post-traumatic stress disorder and its risk factors in Japanese patients living with implantable cardioverter defibrillators: A preliminary examination

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ABSTRACT

Background: Trauma reactions, including post-traumatic stress disorder (PTSD), in patients with implantable cardioverter defibrillators (ICDs) have recently garnered increased attention. The aim of this preliminary study was to examine the incidence of and risk factors for PTSD and to assess its impact on psychosocial distress and health-related quality of life (QOL) in Japanese patients with ICD.

Methods: Seventy-four outpatients with ICD (63 men, 11 women; age 59.3 ± 13.6 years) completed a questionnaire comprising a modified PTSD Checklist Specified for a stressor that included arrhythmias and ICD shocks, the Zung Self-Rating Depression Scale (SDS), the State-Trait Anxiety Inventory (STAI)-State scale, and Medical Outcomes Study 36-item Short-Form (SF-36) for health-related QOL. We compared relevant sociodemographic and medical variables of patients with and without PTSD. The mean number of days since ICD implantation was 2471 ± 703.

Results: Of 74 patients, 28 (37.8%) had received ICDs for secondary prevention, 42 (56.8%) had experienced ICD shocks, 36 (48.6%) had experienced ≥1 appropriate ICD shock, and 12 (16.2%) had experienced electrical storms. We diagnosed 19 patients (25.8%) with PTSD. Compared with the non-PTSD group, the PTSD group had significantly higher SDS and STAI-S scores and significantly lower scores in all eight subscales of the SF-36. Multiple logistic regression analysis identified experiencing ≥1 appropriate ICD shock (odds ratio [OR]: 6.0, 95% confidence interval [CI]: 1.45–24.63, and $p < 0.013$) and anxiolytic use (OR: 15.0, 95% CI: 3.38–66.26, and $p < 0.001$) as independent risk factors for PTSD.

Conclusions: Our study shows that PTSD in patients with ICD has significant psychosocial impact with associated impairment of both physical and mental QOL and suggests that, in particular, patients who experience appropriate ICD shocks or take anxiolytics require psychiatric/psychological intervention.

1. Introduction

Implantable cardioverter defibrillators (ICD) are an established form of therapy for both primary and secondary prevention of lethal cardiac arrhythmias [1]. Previous studies have shown that ICD implantation improves the quality of life (QOL) of most patients with ICD [2,3]. However, underlying diseases or comorbidity, poor social support, or ICD-specific problems such as frequent shocks and poor understanding of ICD therapy can increase anxiety and depressive symptoms and reduce QOL in patients with ICD [2,4,5]. Ten percent to 41% of the patients with ICD experience significant depressive symptoms, whereas general or ICD-specific anxiety occurs in 13–38% [6]. Some preliminary studies have suggested that psychological distress can precipitate arrhythmic events [7,8]. Moreover, a vicious cycle may ensue, characterized by ICD implantation leading to anxiety and depression, which in turn precipitates arrhythmic events, leading to further distress [9].

Recently, trauma reactions, including post-traumatic stress disorder (PTSD), have garnered increased attention as a form of psychosocial distress that partly overlaps depressive symptoms or anxiety in patients with ICD [6,10–18]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [19], PTSD occurs in people who have been exposed to a traumatic event that involves actual or threatened death (criterion A). PTSD symptomatology is categorized into: (1) "intrusive recollection" (persistent re-experiencing of the traumatic event, criterion B); (2) "avoidant/numbing" (persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness that was not present before the trauma, criterion C); and (3) "hyper-arousal" (persistent symptoms of increasing arousal that were not present before the trauma, criterion D).

ICD shocks are potential traumatic stressors in patients with ICD because they may act as continuous reminders of having a potentially fatal disease [10,11]. Traumatic events experienced by patients with ICD vary widely and are complex. Furthermore, even being told that they are at risk for life-threatening arrhythmias that could lead to sudden cardiac death (i.e., ICD implantation for primary prevention) may be traumatic for patients [6]. Therefore, threats to patients' lives and well-being are not isolated events, but are persistent and enduring. Patients with PTSD symptoms may be particularly stressed by agonizing rumination and involuntary preoccupation with the underlying disease process [13].

To our knowledge, five published studies have assessed the incidence of PTSD after ICD implantation and estimated it at 7.6–26% [13–16]. However, these studies used disparate definitions of criterion A of PTSD (i.e., exposure to a traumatic event that involves actual or threatened death), presenting a methodological problem. Some reports classified rapid onset of the cardiac condition (cardiac arrest or acute myocardial infarction) as criterion A [13,15], whereas another used arrhythmia or its treatment (i.e., having an ICD) [14]. In the former, researchers excluded patients receiving ICDs for primary prevention. To cover patients with ICDs for both primary and secondary prevention, we believe that rapid onset of the cardiac condition, life-threatening arrhythmia, and ICD shocks should all separately qualify as meeting criterion A.

The aim of this preliminary study was to examine PTSD incidence and risk factors and to assess its impact on psychosocial distress and health-related QOL of Japanese patients with ICD.

2. Method

2.1. Participants and procedures

This preliminary study was conducted as a component of routine care in a clinical setting where patients with ICD had been recognized as experiencing psychosocial difficulties. During the 4 months from February to May, 2006, collaborative care between cardiologists and psychologists was offered to patients attending the ICD clinic of the Department of Cardiology, Tokyo Women's Medical University. During this period, psychologists assessed patients with ICD for psychosocial problems. Informed consent for this assessment was obtained from all participating patients; all were aged over 18 years and able to communicate in Japanese. The patients completed self-completing questionnaires (in the same order for all patients) to assess the psychological and health-related factors under investigation on the same day as their cardiological assessment. To ensure that they did not miss any questions and to help them understand the items, an experienced psychologist (S.K.) was present while the patients completed the questionnaires, which took 20–30 min. Where psychosocial problems were suspected, the psychologist recommended that the participant receive psychosocial care. The 72 patients who completed their questionnaires during the study period were retrospectively evaluated.

2.2. Measures

2.2.1. Assessment of post-traumatic stress symptoms

PTSD symptoms were assessed with a modified PTSD Checklist Specified for a stressor (PCL-S) [20]. The specified stressor was "potentially fatal cardiac arrhythmias or ICD shocks, both appropriate and inappropriate". The PCL-S is a widely used, self-reporting, extensively validated 17-item Likert scale that corresponds to the DSM-IV [19] criteria for PTSD. Participants were asked to rate specific PTSD symptoms resulting from their potentially fatal cardiac arrhythmias or ICD shocks. To make the PCL-S easier to complete, the checklist was modified from a 5-point ("not at all", "a little bit", "moderately", "quite a bit", and "extremely") to a four-point response scale ("not at all or a little of the time", "some of the time", "good part of the time", and "most of the time") to match the format of the other questionnaires. A presumptive PTSD diagnosis was made when a participant met the DSM-IV symptom criteria, namely, at least one item from criterion B (intrusive recollection), three items from criterion C (avoidant/numbing), and two items from criterion D (hyper-arousal). Symptoms those were rated as "some of the time" or above (responses three through four for individual items) were classified as present.

2.2.2. Assessment of other psychological/health-related variables

The Zung Self-Rating Depression Scale (SDS) was used to screen for depression and to measure the severity of the depression in numerous settings [21]. The SDS is a self-reporting scale for assessing the psychological and somatic symptoms of depression. It contains 20 questions and is used to assess depression in clinical studies on cardiovascular disease [22,23].

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms [24]. As state anxiety is characterized as a temporary change in a patient's emotional state due to medical illness or other external cause and because state anxiety has previously been used in clinical studies on cardiovascular disease [25,26], only the state scale measurement was used in this study. STAI scores range 20–80; higher scores indicate greater degrees of anxiety.

The Medical Outcomes Study 36-item Short-Form (SF-36) [27,28] was used to assess health-related QOL. This is a widely used self-reporting measure of general physical and mental health functioning across eight domains that include physical functioning; role-physical (limitations in the kinds/amount of work/activities due to physical functioning); bodily pain; general health; vitality; social functioning; role-emotional (limitations in the kinds/amount of work/activities due to emotional functioning); and mental health. Higher scores are indicative of greater health-related QOL. A number of validation studies have been conducted in the general and various medically ill populations. The Japanese version has demonstrated good reliability and validity in the general population of Japan [27,28].

2.3. Clinical variables associated with implantable cardioverter defibrillators

Data on the relevant clinical characteristics of the participants and the conditions under which their ICDs were implanted were obtained from medical records. The collected data included indications for ICDs, underlying heart disease, New York Heart Association functional class, shock therapy history (times of shocks, both appropriate and inappropriate; electrical storm [ES] experiences, defined as the occurrence of ≥3 separate episodes of ventricular tachycardia or ventricular fibrillation within 24 h; days since ICD implantation; days since last shock), medications, living with/without family, and employment status.

2.4. Statistical analyses

Student's *t*-test was used to identify differences in continuous variables between groups, and categorical variables were compared by the χ^2 test. To identify independent risk factors for PTSD, the variables were analyzed in two steps. In the first step, univariate analysis was performed. In the second step, multiple logistic regression analysis was performed, with forward stepwise

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variable selection. In the regression analysis, data sets that were significantly ($p < 0.05$) or almost significantly ($p < 0.25$) associated with the PTSD group were used in the first step. Regression coefficients were used to calculate the odds ratio (OR) and 95% confidence interval (CI) of the OR. In all statistical analyses, $p < 0.05$ was taken to indicate statistical significance. Data analyses were performed by using SPSS (version 16, SPSS, Chicago, IL, USA).

3. Results

3.1. Relevant clinical and other characteristics of participants

The relevant clinical and other characteristics of the study group are listed in Table 1. In all, 74 patients (63 men and 11 women; age, 59 ± 14 years [mean ± SD]) completed the surveys. Eight patients (11%) lived alone and 35 (47%) were not working at the time of the survey. The underlying heart disease was coronary artery disease in 19% of cases. Twenty-eight patients (38%) underwent ICD implantation for secondary prevention. The mean number of days since ICD implantation was 2471 ± 703 days. Of the 74 patients, 42 (57%) had experienced ICD shocks and 12 (16%), ES. No patients in had received non-pharmacological therapy, such as cognitive behavioral therapy (CBT), for any psychiatric condition.

3.2. Incidence of post-traumatic stress disorder and its effect on psychological distress and health-related quality of life

Nineteen of the 74 patients (25.8%) were diagnosed with PTSD. The incidence of PTSD according to the indication for ICD and ICD shock experience is shown in Fig. 1. No differences in incidence of PTSD were found between patients who received ICD for primary prevention and those who received ICD for secondary prevention (Table 1). Remarkably, of the 21 patients with ICDs for primary prevention who had never experienced ICD shocks, four (21.1%) were diagnosed with PTSD.

Analyses of SDS and STAI-S scores as well as the eight subscales of the SF-36 are shown in Table 2. Compared with the non-PTSD group, the PTSD group had significantly higher SDS and STAI-S scores and significantly lower scores in all eight subscales of the SF-36.

3.3. Risk factors for post-traumatic stress disorder

Table 1 also lists the results of the univariate analysis performed in the first step to identify risk factors for PTSD. Compared with the non-PTSD group, the PTSD group had significantly higher New York Heart Association functional class ($p < 0.028$), more frequent ES ($p < 0.001$), experienced ≥1 appropriate ICD shocks ($p < 0.01$), and more frequent use of antidepressants ($p < 0.05$) and anxiolytics ($p < 0.0001$). According to multiple logistic regression analysis, experiencing ≥1 appropriate ICD shock and anxiolytic use were significant independent risk factors (Table 3). The OR for experiencing ≥1 appropriate ICD shock was 6.0 (95% CI: 1.45–24.63, and $p < 0.013$); that for anxiolytic use was 15.0 (95% CI: 3.38–66.26, and $p < 0.001$).

Table 1
Characteristics of subjects with or without PTSD.

	Overall (n=74)	PTSD (n=19)	No PTSD (n=55)	p
Male	63(85.1)	18(94.7)	45(81.8)	0.16
Age in years	59.3 ± 13.6	61.3 ± 11.8	58.6 ± 14.2	0.47
Indication for ICD				
Primary prevention	46(62.2)	14(73.7)	32(58.2)	
Secondary prevention	28(37.8)	5(26.3)	23(41.8)	0.18
Underlying heart disease				
Coronary artery disease	14(18.9)	4(21.1)	10(18.2)	
Idiopathic dilated cardiomyopathy	14(18.9)	5(26.3)	9(16.4)	
Hypertrophic cardiomyopathy	11(14.9)	4(21.1)	7(12.7)	
Arrhythmogenic right ventricular cardiomyopathy	2(2.7)	0(0.0)	2(3.6)	
Unclassified cardiomyopathy	2(2.8)	1(5.3)	1(1.8)	
Valvular heart disease	3(4.1)	2(10.5)	1(1.8)	
Idiopathic VF/long QT syndrome	22(29.7)	3(15.8)	19(34.5)	
Others	6(8.1)	0(0.0)	6(10.9)	0.28
NYHA functional class				
I	51(68.9)	10(52.6)	41(74.5)	
II	22(29.7)	8(42.1)	14(25.5)	
III	1(1.4)	1(5.3)	0(0.0)	0.03
Clinical variance				
≥1 ICD shock, total*	42(56.8)	14(73.7)	28(50.9)	0.07
≥1 ICD shock, appropriate	36(48.6)	14(73.7)	22(40.0)	0.01
≥1 ICD shock, inappropriate, never appropriate	6(8.1)	0(0.0)	6(10.9)	0.33
Number of shocks (in those receiving shocks)	13.5(21.7)	12.3(22.2)	6.1(15.6)	0.13
≥1 Electrical storm	12(16.2)	8(42.1)	4(7.2)	0.00
Days since ICD implantation	2471.2 ± 702.5	2519 ± 727.5	2454 ± 699.6	0.73
Days since last shock		806.4 ± 749.6	1226 ± 1018.3	0.18
Medications				
β-Blockers	35(47.3)	10(52.6)	25(45.5)	0.39
ACE inhibitors/ARBs	36(48.6)	9(47.4)	27(49.1)	0.56
Amiodarone/sotalol	34(37.8)	11(57.9)	23(41.8)	0.17
Antidepressants	4(5.4)	3(15.8)	1(1.8)	0.05
Anxiolytics	15(20.3)	10(52.6)	5(9.1)	0.00
Hypnotics	10(13.5)	5(26.3)	5(9.1)	0.07
Not living with family	8(10.8)	3(15.8)	5(9.1)	0.33
Unemployed/retired	35(47.3)	13(68.4)	22(40.0)	0.09

Values indicate number of patients (%) or the mean ± SD.
ACE, angiotensin-converting enzyme; ARB, angiotension II receptor blocker; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; PTSD, post-traumatic stress disorder; and VF, ventricular fibrillation.
* Appropriate and inappropriate shocks.

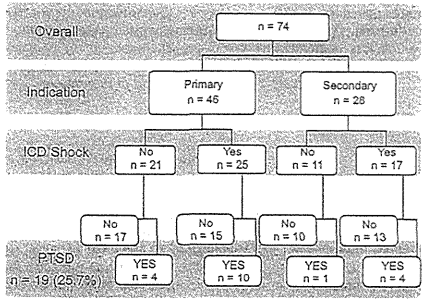

Fig. 1. The prevalence of PTSD according to indications for ICD and ICD shock experience. ICD, implantable cardioverter defibrillator and PTSD, post-traumatic stress disorder.

Table 2
Scores for psychological distress and health-related QOL with and without PTSD.

	Overall (n=74)	PTSD (n=19)	No PTSD (n=55)	t	p
SDS	39.7 ± 10.4	48.5 ± 8.4	36.3 ± 9.1	5.05	0.00
STAI-state	41.6 ± 12.7	49.1 ± 14.0	39.0 ± 11.2	3.17	0.00
SF-36					
Physical functioning	71.5 ± 22.3	61.9 ± 17.5	74.6 ± 22.9	−2.15	0.04
Role physical	73.5 ± 27.2	57.0 ± 28.8	79.1 ± 24.5	−3.17	0.00
Bodily pain	74.9 ± 25.0	65.8 ± 22.7	77.9 ± 25.2	−1.81	0.08
General health	46.5 ± 19.0	32.4 ± 15.2	51.1 ± 17.9	−3.98	0.00
Vitality	58.9 ± 19.8	47.4 ± 16.3	62.4 ± 19.5	−2.86	0.01
Social functioning	71.1 ± 27.0	52.1 ± 28.8	77.3 ± 23.5	−3.73	0.00
Role emotional	74.6 ± 26.6	56.9 ± 26.4	80.8 ± 24.1	−3.53	0.00
Mental health	70.7 ± 21.3	52.2 ± 18.0	76.7 ± 18.6	−4.85	0.00

PTSD, post-traumatic stress disorder; SDS, Zung Self-Rating Depression Scale; SF-36, Medical Outcomes Study 36-item Short-Form; and STAI, State-Trait Anxiety Inventory.

4. Discussion

This cross-sectional study obtained three major findings. First, the incidence of PTSD, estimated by using the modified PCL-S for cardiac arrhythmia or ICD shock, was 25.8% in Japanese patients with ICD. Second, the PTSD was associated with significantly impaired QOL in patients with ICD for both physical and mental subscales. Third, independent risk factors for PTSD were experiencing ≥1 appropriate ICD shock and anxiolytic use. To our knowledge, this is the first study to evaluate PTSD in Japanese patients with ICD.

Table 3
Logistic regression analysis of risk factors for PTSD.

Variable	B	p	Odds ratio	95% Confidence interval
Anxiolytic use	2.706	0.013	14.98	3.38–66.26
≥1 appropriate ICD shock	1.787	0.000	5.97	1.45–24.63

−2 log likelihood = 62.092; $\chi^2 = 22.214$ ($p < 0.0001$); and Nagelkerke $R^2 = 0.381$.
PTSD, Post-traumatic stress disorder and ICD, implantable cardioverter defibrillator.

4.1. Incidence of post-traumatic stress disorder in patients with implantable cardioverter defibrillators

Five studies estimated the incidence of PTSD in patients with ICD to be 7.6–26% [13–17]. This variation may be caused by several factors, including PTSD diagnostic procedure and study population characteristics such as underlying disease. In the United States, the underlying diseases in 81% of patients with ICD are ischemic heart diseases such as myocardial infarction or angina pectoris, whereas in Japan, the underlying diseases in patients with ICD are ischemic heart diseases, cardiomyopathies, and idiopathic ventricular fibrillation (arrhythmia) in 34%, 35%, and 19%, respectively [29]. In the present study, 38% of the participants received ICDs for secondary prevention. Of the 28 patients who received ICDs for secondary prevention, five developed PTSD. This finding appears consistent with those of previous studies of patients with ICDs for secondary prevention: 26% in the Living with an Implanted Cardioverter Defibrillator study [13] or 19% at baseline (average of 2 years after implantation) and 12% at final follow-up (5.5 years) in a longitudinal study [15]. As was true of our study, Kapa et al. studied patients with ICD with both primary and secondary prevention indications (51% for secondary) [14]. They found that the incidence of PTSD at 2, 6, and 12 months after implantation was 21%, 12%, and 13%, respectively.

The diagnostic procedure for PTSD also affects the apparent incidence of PTSD. It remains controversial whether patients who have received ICDs for primary prevention and have not experienced ICD shocks meet criterion A for a PTSD diagnosis (exposure to a traumatic and life-threatening event) [19]. However, in the present study, 4/21 (19%) of such patients did develop PTSD. Despite the small number of subjects, this finding suggests that even being told that they are at risk of life-threatening arrhythmias and having an ICD implanted may result in the development of PTSD symptoms in some patients. PTSD occurring after receiving diagnoses of other life-threatening diseases such as HIV [30] has been reported.

The gold standard for diagnosing PTSD is a structured clinical interview such as the Clinician-Administered PTSD Scale [31]. However, in all previous studies evaluating PTSD in patients with ICD, self-reporting questionnaires such as the Impact of Events Scale-Revised [13–15,32] or the Post-traumatic Stress Diagnostic Scale [16,17,33] have been used to make a presumptive diagnosis. Although the PCL-S used in this study reflects the DSM-IV symptoms of PTSD, it also provides only a presumptive diagnosis. Further studies using a structured interview procedure for a more accurate PTSD diagnosis are needed.

4.2. Factors associated with post-traumatic stress disorder

The following key risk factors for depression or anxiety in patients with ICD have been identified: < 50 years of age, being female, premorbid psychiatric diagnosis, poor social support, and > 5 defibrillations (appropriate or inappropriate) [6]. However, information on the risk factors for PTSD in such patients has been limited.

Table 4
PTSD symptom clusters and presentation in patients with ICD[c].

Criterion A (exposure): All
• Cardiac event, SCA[a], ICD[b] implantation, shock, or electrical storm is perceived as deadly or threatening
• There is a perception of fear, helplessness, or horror
Criterion B (persistent re-experiencing): ≥1
• Recalling the cardiac event repeatedly
• Dreaming about getting shocked
• Truly believing or feeling shock is recurring (e.g., phantom shock)
• Exposure to cues that remind them of the event (e.g., couch they were on when shocked) creates psychological distress
• Exposure to cues that remind them of the event (e.g. heart racing) causes the body to react
Criterion C (persistent avoidance): ≥3
• Avoiding discussion of the event (this may include avoidance of an office visit or repeated no-shows)
• Cannot remember the event (e.g., SCA or shock)
• Avoidance of engagement in activities because of fear of shock
• Feeling estranged from family or friends following cardiac trauma
• Restricted range of affect (inability to express a range of emotions) following SCA or shock
• Belief that shock is an indicator of cardiac health and foreshortened future
Criterion D (increased arousal): ≥2
• Following cardiac trauma (e.g., surgery, SCA, shock, electrical storm)
◦ *Trouble falling or staying asleep*
◦ More irritable and angry
◦ Difficulty concentrating
◦ Exaggerated startle response
• Hyper-vigilant: preoccupied with heart rate, gastrointestinal and chest pain, and other bodily sensations

[a] SCA, sudden cardiac arrest.
[b] ICD, implantable cardioverter-defibrillator.
[c] Modified from Sears et al. [6].

The effect of ICD shocks on the development of PTSD has been evaluated in five studies [13–17]; their findings are controversial. In three of the five studies, ICD shocks were associated with PTSD diagnoses [14–16]. Kapa et al. found that patients who had experienced ES had significantly higher PTSD scores within 2 months after implantation; however, they reported no difference in PTSD scores between patients who had experienced appropriate ICD shocks and those who had not [14]. Von Kanel et al. found that experiencing at least five ICD shocks (appropriate or inappropriate) was a predictor of PTSD [15]. Versteeg et al. found that ICD shock (appropriate or inappropriate) was the strongest determinant of PTSD at 3 months post-implantation, but was not associated with PTSD at 6 months post-implantation.

The role of inappropriate ICD shocks on the development of PTSD was not evaluated in the five studies mentioned above [13–17]. In the present study, inappropriate ICD shocks were not associated with PTSD. Due to the possibility of various backgrounds being associated with the development of PTSD, a more accurate role of ICD therapy as the cause of PTSD should be evaluated in different study designs, including a control population.

Psychological distress, especially PTSD symptoms, evokes sympathetic nervous system activity, which might be a trigger for a lethal arrhythmia. Although depression has been reported as a predictor for appropriate shocks (subsequent occurrence of lethal arrhythmias) among patients with ICD [34]; such a predictive effect of PTSD remains unknown. In the present study, experiencing ≥1 appropriate ICD shock was associated with PTSD, but a causal relationship cannot be inferred from this cross-sectional study.

In addition, we identified anxiolytic use as an independent risk factor. Versteeg et al. and Habibovic et al. found that baseline anxiety predicts PTSD independently [16,17]. Subjective cardiac symptoms [13] or ICD concerns [16] are reportedly associated with PTSD. It is reasonable to presume that anxiety or perceived sensitivity to cardiac conditions may lead to the subsequent prescription of anxiolytics. First-line standard pharmacologic treatment for PTSD is a selective serotonin reuptake inhibitor (SSRI), not an anxiolytic [35]. Furthermore, non-pharmacologic treatment such as CBT is generally effective for PTSD [36], and may be useful for patients with ICD [37,38]. Although the effect of SSRIs on decreasing ICD intervention is unknown, preliminary studies have reported that a SSRI [39] or SSRI in combination with CBT [40] is associated with reduced ventricular arrhythmia in patients with ICD.

Clinicians need to consider the possibility of PTSD; it is desirable to consult psychiatrists when it is suspected. We have provided examples of how PTSD symptoms may be expressed in patients with ICD according to the description of Sears et al. [6] (Table 4). Formal diagnosis requires that the disturbance (symptoms in criteria B, C, and D) last longer than 1 month and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning [19].

4.3. Limitations of this study

This preliminary study has several limitations. First, there were possible design flaws in that it did not enroll consecutive patients, which may have created bias. Moreover, it was retrospective, of cross-sectional design, and involved a single center. Second, we used a modified version of the PCL-S, a self-reporting questionnaire, as a diagnostic tool. As explained in Section 4.1, this tool only provides a presumptive diagnosis. Furthermore, modification of the PCL-S may have influenced its discriminant properties. Third, because the number of subjects in this study was relatively small, subgroup analysis was not feasible. To clarify these issues, we suggest that further prospective clinical investigations, including a control population, must be carried out.

5. Conclusions

The present preliminary study shows that PTSD has a significant psychosocial impact with associated impairment of both physical and mental QOL in patients with ICD. In particular, our findings suggest that patients who have experienced appropriate ICD shocks or are taking anxiolytics require psychiatric/psychological intervention.

Conflict of interest

None of the authors has any conflicts of interest to declare.

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Original article

Impact of clustered depression and anxiety on mortality and rehospitalization in patients with heart failure☆

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ABSTRACT

Background: Anxiety is often present in patients with depression. The aim of this study was to evaluate the impact of clustered depression and anxiety on mortality and rehospitalization in hospitalized patients with heart failure (HF).

Methods: A total of 221 hospitalized patients with HF, who completed the questionnaires, were analyzed in this prospective study (mean age 62 ± 13 years; 28% female). One-third patients had implanted cardiac devices. Depression was defined as a Zung Self-Rating Depression Scale index score of ≥60 and anxiety was defined as a State-Trait Anxiety Inventory score of ≥40 (male) or ≥42 (female). The primary outcome was the composite of death from any cause or rehospitalization due to worsened HF and refractory arrhythmia.

Results: Of the 221 HF patients, 29 (13%) had depression alone, 80 (36%) had anxiety alone, and 46 patients (21%) had both depression and anxiety. During an average follow-up of 41 ± 21 months, patients with depression alone and those with clustered depression and anxiety were at an increased risk of the primary outcome [hazard ratio (HR) 2.24, 95% confidence interval (CI): 1.17–4.28, $p = 0.01$ and HR 2.75, 95% CI: 1.51–4.99, $p = 0.01$, respectively] compared to patients with no symptoms. Multivariate analysis after adjusting for age, gender, New York Heart Association functional class, B-type natriuretic peptide, device implantation, renal dysfunction, and left ventricular dysfunction showed clustered depression and anxiety, but not depression alone or anxiety alone, was an independent predictor of the primary outcome (HR 1.96, 95% CI: 1.00–3.27, $p = 0.04$).

Conclusions: Our results showed that clustered depression and anxiety were associated with worse outcomes in patients with HF.

Introduction

Heart failure (HF) is caused from most types of heart diseases and is a chronic and progressive condition that is a major cause of morbidity and mortality [1]. The psychological issues, particularly emotional distress including depression and anxiety, are common in patients with HF [1–5]. Several studies have focused on the role of depression and suggested that depression is a possible risk factor for adverse outcomes in patients with HF [4–7]. The prevalence of depression is reported to be approximately 15–40% in patients with HF, and depression is independently associated with poor outcomes [5–13]. A meta-analysis showed that depression is common among patients with HF, and substantially higher rates of clinically significant depression are present among patients with more severe HF [4].

There have been fewer studies regarding anxiety in patients with HF. A previous report showed that 18.4% of patients with HF had an anxiety disorder [14]. Another report showed that the score for anxiety symptoms was higher in patients with HF than in healthy controls [15]. However, this issue has remained controversial [1]. In some studies, no association has been found between anxiety symptoms and cardiac events in patients with HF [16–19].

Recently, van den Broek et al. [20] focused on the impact of clustering psychosocial risk factors on clinical outcomes in patients with implantable cardioverter defibrillators (ICDs) and showed that ICD patients with both anxiety and Type D personality were at an increased risk of ventricular arrhythmia. In that study, the risk factors were clustered because psychological risk factors often occurred together, but not individually, and the clustering of psychological risk factors may pose a high-risk factor for clinical events than would a single risk factor in cardiac patients [20,21]. Although depression and anxiety have been discussed separately as psychological factors, they frequently cluster within a patient [22]. The signs and symptoms of anxiety are often present in patients with depression, and the two conditions may play a partial role in a pathophysiological process of HF [23]. Some studies have shown that the clustered depression and anxiety worsened patients' health status following myocardial infarction or percutaneous coronary intervention [24,25]. From this viewpoint, clustered depression and anxiety may be clinically valuable as an indicator of psychological distress in patients with HF. However, a few studies have investigated this issue. The aim of this study was to evaluate the effect of clustered depression and anxiety on mortality and rehospitalization in patients with HF.

Methods

We conducted a substudy of the prospective observational study comprising hospitalized patients with cardiovascular disease, who were admitted to the Cardiology Department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions (e.g. unconsciousness, intensive care, and end stage of another life-threatening disease) that make completing self-reported written questionnaires difficult were excluded. Among them, 221 patients with a New York Heart Association (NYHA) functional class ≥2 on admission, who were diagnosed with HF, and who completed the questionnaires were included in this study (Fig. 1). The details of the study have been reported elsewhere [26]. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

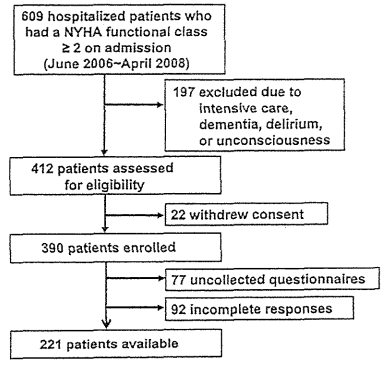

Fig. 1. The flow diagram of study subjects. NYHA, New York Heart Association.

Assessment of depression and anxiety

The majority of patients received the psychological questionnaires within 3 days (2 ± 1 days) after their admission to the hospital. For patients who initially required intensive treatment, these questionnaires were received after their transfer to the general cardiology ward. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression and to measure the severity of the depression in a number of settings [27–31]. The Zung SDS is a self-reported scale containing 20 questions that assess the psychological and somatic symptoms. The Zung SDS score has been reported to be a primary discriminating variable in distinguishing depressed from non-depressed persons and indicates likelihood ratio positive for major depression as 3.3 [95% confidence interval (CI): 1.3–8.1] and likelihood ratio negative as 0.35 (95% CI: 0.2–0.8) [29]. The Zung SDS score has also been used to assess depression in clinical studies on cardiovascular diseases [32–36]. A cutoff index score of 60 has been shown to detect clinical depression while avoiding an abundance of false positives in sick patients [37–40]. In this study, depression was defined as a Zung SDS index score of ≥60.

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms [41]. In this study, only the state-scale measurement was used because state anxiety is characterized as a temporary change in each patient's emotional state due to medical illness or other external cause, the measurement has also been used in clinical studies on cardiovascular diseases [16,20,42]. The STAI comprises 20 items, and each item is scored on a four-point scale from 1 (not at all) to 4 (very much so). The STAI scores range from 20 to 80, with higher scores indicating greater levels of anxiety. Anxiety was defined as a score of ≥40 (male) or ≥42 (female) [43,44].

Follow-up

After discharge, patients were seen as outpatients at our hospital or their general practitioner's clinic at 1- to 3-month intervals until October 2011. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT), and ICD, were also followed every 3–6 months at our pacemaker/ICD clinic. The information about deceased patients was obtained from the medical records, family members, their general practitioners, and the admitting hospital.

Clinical outcomes

The primary outcome was the composite of death from any cause and rehospitalization due to worsened HF and refractory arrhythmia from the time of enrollment to the first event. Worsened HF was defined by signs and symptoms, such as dyspnea, rales, and ankle edema, as well as by the need for treatment with diuretics, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia that required external defibrillation or pacing, intravenous antiarrhythmics, such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, or bradyarrhythmia that required implantation of a pacemaker. Both supraventricular and ventricular arrhythmias are common in patients with HF, and cause symptoms, hemodynamic instability, and morbidities such as stroke and sudden death. Therefore, we included rehospitalization for refractory arrhythmia in

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the primary endpoint. The second outcome was death from any cause.

Data analysis

The data are presented as either mean ± standard deviation (SD) or number of patients. We created four groups on the basis of depression and anxiety: (1) depression alone, (2) anxiety alone, (3) clustered depression and anxiety, and (4) no symptoms (no depression nor anxiety). Baseline clinical data were compared between the groups using analysis of variance (ANOVA). The Cox proportional hazards model was used to assess the relationship of depression, anxiety, and the cluster of both with clinical outcomes. We first assessed the unadjusted relationship of the following variables at discharge with the primary outcome: female gender, age ≥65 years, NYHA functional class, plasma B-type natriuretic peptide (BNP) concentration >250 pg/ml [45,46], implantation of an ICD/CRT with a defibrillator (CRT-D), left ventricular ejection fraction (LVEF) ≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula [47] <60 ml/min/1.73 m^2, depression, anxiety, and clustered depression and anxiety. Then, we assessed the relationship of depression, anxiety, and the cluster of both with the primary outcome after controlling for gender, age ≥65 years, NYHA functional class, BNP >250 pg/ml, implantation of an ICD/CRT-D, LVEF ≤35%, and eGFR <60 ml/min/1.73 m^2. The cumulative event-free rates were calculated using the Kaplan–Meier method. The data analyses were performed with SPSS (Statistical Package for the Social Sciences) statistical software (version 11.01, SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

Patients

A total of 221 patients with HF who completed both the Zung SDS and STAI were included in this analysis. More than half of the patients (64%) had a non-ischemic etiology, and one-third had implanted cardiac devices. Five patients (2%) who were diagnosed with major depression by a psychiatrist had taken antidepressants (Table 1). In our sample, none of the patients with depression received non-pharmacological treatment such as cognitive behavior therapy.

Psychological distress and outcomes

Overall, 75 patients (34%) were diagnosed as having depression and 126 patients (57%) as having anxiety. Among them, 29 patients (13%) had depression alone, 80 patients (36%) had anxiety alone, and 46 patients (21%) had both depression and anxiety (Table 1).

During an average follow-up of 41 ± 21 months, 69 patients (31%) met the primary outcome: 31 patients died and 38 patients required rehospitalization due to worsened HF or refractory arrhythmia. Kaplan–Meier curves for the primary outcome in the four groups are shown in Fig. 2. Patients with depression alone and those with clustered depression and anxiety were at an increased risk of the primary outcome [hazard ratio (HR) 2.24, 95% CI: 1.17–4.28, $p = 0.01$ and HR 2.75, 95% CI: 1.51–4.99, $p = 0.01$, respectively] compared to patients with no symptoms. Causes of death and rehospitalization are shown in Table 2. Kaplan–Meier curves for death from any cause are shown in Fig. 3. Patients with clustered depression and anxiety were at an increased risk of death

Table 1
Patient characteristics.

	Depression alone ($n = 29$)	Anxiety alone ($n = 80$)	Depression + anxiety ($n = 46$)	No symptoms ($n = 66$)	p value
Age (years)	61 ± 10	62 ± 14	60 ± 12	62 ± 12	0.18
Female	7 (24%)	22 (28%)	14 (30%)	19 (25%)	0.91
Underlying heart disease					0.01
Coronary artery disease	7 (24%)	20 (25%)	5 (11%)	39 (59%)	
Non-ischemic cardiomyopathy	11 (38%)	23 (29%)	37 (80%)	44 (67%)	
Valvular heart disease	10 (34%)	20 (25%)	2 (4%)	7 (11%)	
Congenital heart disease	0 (0%)	1 (1%)	2 (4%)	2 (3%)	
BNP on admission (pg/ml)	269 (84–709)	275 (4–2254)	349 (8–5271)	152 (4–8454)	0.01
BNP at discharge (pg/ml)	236 (48–826)	242 (18–1478)	288 (15–2326)	120 (5–4926)	0.01
NYHA functional class on admission (II/III/IV)	25/4/0	67/15/0	23/22/1	56/10/0	<0.01
NYHA functional class at discharge (II/III/IV)	27/2/0	77/3/0	30/15/1	64/2/0	<0.01
LVEF (%)	35 ± 10	38 ± 12	35 ± 15	39 ± 16	0.21
eGFR (ml/min/1.73 m^2)	72 ± 36	76 ± 38	70 ± 43	80 ± 38	0.16
Implanted cardiac devices					
Pacemaker/CRT-P	3 (10%)	5 (6%)	7 (15%)	7 (11%)	0.20
ICD/CRT-D	7 (24%)	18 (23%)	15 (33%)	15 (23%)	0.16
Comorbidities					
Hypertension	10 (34%)	31 (39%)	18 (39%)	25 (38%)	0.16
Diabetes	3 (10%)	27 (34%)	11 (24%)	28 (42%)	0.05
Major depression	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.04
Medications at discharge					
Beta-blockers	21 (72%)	59 (74%)	33 (72%)	43 (65%)	0.76
ACE inhibitors/ARBs	25 (86%)	69 (86%)	42 (91%)	59 (89%)	0.57
Spironolactone/eplerenone	16 (55%)	38 (48%)	30 (65%)	31 (47%)	0.15
Calcium channel blockers	16 (55%)	55 (69%)	19 (41%)	43 (65%)	<0.01
Aspirin	10 (34%)	29 (36%)	15 (33%)	33 (50%)	0.09
Warfarin	16 (55%)	42 (53%)	32 (70%)	22 (33%)	0.11
Amiodarone	11 (38%)	22 (28%)	20 (43%)	9 (14%)	<0.01
Antidepressants	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.16
Married	26 (90%)	73 (91%)	36 (78%)	64 (97%)	<0.01
Employed	13 (45%)	40 (50%)	13 (28%)	34 (52%)	0.04

Values are n (%) or mean ± SD or median (range).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CRT-D, CRT with a defibrillator; CRT-P, CRT with a pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

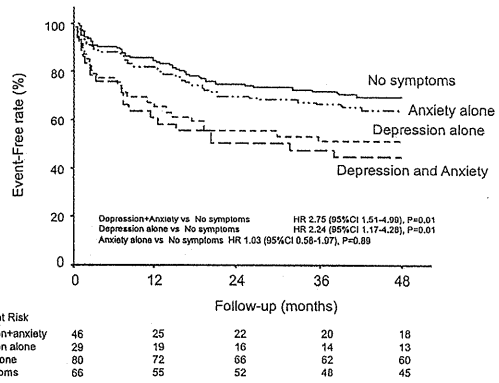

Fig. 2. Kaplan–Meier curve for the primary outcome (death from any cause or rehospitalization due to worsened heart failure or refractory arrhythmia) in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

Table 2
Causes of death and rehospitalization for cardiac events.

	Depression alone ($n = 29$)	Anxiety alone ($n = 80$)	Depression + anxiety ($n = 46$)	No symptoms ($n = 66$)	p value
Death from any cause	8 (28%)	4 (5%)	17 (37%)	2 (3%)	<0.01
Cardiac death	8 (28%)	4 (5%)	16 (35%)	2 (3%)	<0.01
Sudden death	2 (7%)	1 (1%)	1 (2%)	0 (0%)	0.96
Heart failure	6 (21%)	3 (4%)	15 (33%)	2 (3%)	<0.01
Non-cardiac death	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0.06
Hospitalization for heart failure	7 (24%)	15 (19%)	5 (11%)	4 (6%)	0.90
Hospitalization for refractory arrhythmia	3 (10%)	2 (3%)	1 (2%)	1 (2%)	0.29

Values are n (%).

from any cause (HR 5.59, 95% CI: 2.84–10.90, $p < 0.01$) compared to patients with no symptoms.

The univariate analysis showed that in addition to NYHA functional class, implantation of an ICD/CRT-D, LVEF ≤35%, BNP at discharge >250 pg/ml, eGFR <60 ml/min/1.73 m^2, depression alone, and a combination of depression and anxiety, but not anxiety alone, were significant predictors for the primary outcome (Table 3).

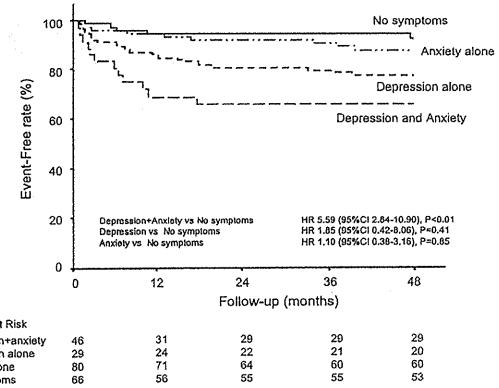

Fig. 3. Kaplan–Meier curve for death from any cause in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

Table 3
Univariate predictors for the primary outcome.

	Hazard ratio (95% CI)	p value
Female gender	0.70 (0.43–1.15)	0.16
Age ≥65 years	0.89 (0.56–1.42)	0.64
NYHA functional class at discharge	3.97 (2.61–6.04)	<0.01
Implantation of an ICD/CRT-D	4.26 (2.56–7.07)	<0.01
eGFR <60 ml/min/1.73 m^2	2.88 (1.81–4.59)	<0.01
BNP at discharge >250 pg/ml	2.95 (1.80–4.81)	<0.01
LVEF ≤35%	1.99 (1.24–3.19)	<0.01
Depression	2.59 (1.56–4.20)	<0.01
Anxiety	1.71 (0.98–2.98)	0.05
Depression and anxiety	2.63 (1.56–4.41)	<0.01

BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy with a defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 4
Relationship of depression and anxiety with the primary outcome after adjusting for age, gender, New York Heart Association class, device implantation, estimated glomerular filtration rate, B-type natriuretic peptide, and left ventricular ejection fraction.

	Hazard ratio (95% CI)	p value
Depression	1.69 (0.97–2.95)	0.06
Anxiety	1.46 (0.80–2.65)	0.21
Depression and anxiety	1.96 (1.00–3.27)	0.04

The relationship between depression and anxiety with the primary outcome after adjusting for age, gender, NYHA class, device implantation, eGFR, BNP, and LVEF revealed that patients with clustered depression and anxiety had an increased risk of the primary outcome, but depression alone was not related to the primary outcome (Table 4).

Discussion

Our study revealed that the prevalence of clustered depression and anxiety was 20% in hospitalized patients with HF. Furthermore, we found that patients with both depression and anxiety were at an increased risk of the primary composite outcome: death from any cause and rehospitalization due to worsened HF and refractory arrhythmia. Finally, clustered depression and anxiety, but not depression or anxiety alone, were shown to be independent factors associated with worsening clinical outcomes.

Several studies have shown that depression is an independent predictor of mortality in patients with HF [1–13]. In our study, depression was a risk factor in the univariate analysis but was not an independent factor after adjusting for clinical variables at discharge related to the primary outcome. There are a number of possible reasons for the differences in our results compared with those in the previous reports. First, our study had a high prevalence (one-third) of patients with an ICD/CRT-D. At present, an ICD is the principle therapy in HF patients for preventing sudden cardiac death. It is increasingly used due to the extended indication for primary prevention. However, ICD-specific problems, such as frequent shocks and a poor understanding of ICD therapy, increase depressive symptoms and reduce the quality of life for the ICD patients [39,48–50]. Our main study showed that an ICD implantation was significantly associated with depression [26]. Furthermore, the prevalence of depression increased as the NYHA functional class grade increased [4]. In our study, 18 of 23 patients (78%) with NYHA class III/IV at discharge were diagnosed with depression by the Zung SDS. The presence of an ICD/CRT-D and NYHA functional class III/IV may have confounded the association between depression and the primary outcome. Therefore, depression alone was thought not to be a predictor in this study after adjusting for multiple variables.

State anxiety is a transient mental or emotional reaction to several stressors, including medical illness. In a sense, it is thought to be a normal reaction in hospitalized patients and an inevitable result of hospitalization. A Japanese report showed that anxiety has been reported to be independently associated with rehospitalization due to worsened HF in outpatients with stable HF [44]. However, in general, an association between anxiety and mortality or long-term cardiac events in patients with HF has not been found [16–19]. Katon et al. suggested that the combination of depression and anxiety is associated with poor treatment adherence and increased medical complications in patients with chronic medical illness, which may be a severe consequence [51]. Anxiety and depression are different disorders, and the way in which their mechanisms may interact in the development of cardiac events or death are not understood. In the real world, however, psychological factors may cluster together within individuals to increase the risk of subsequent medical events [21]. There is a possibility that patients with higher psychological distress are selected by combining anxiety with depression.

In our study, HF was a major cause of death, and the rate of HF was significantly higher in patients with both depression and anxiety than in those with either depression or anxiety only or those with no symptoms. Although its pathophysiologic mechanisms are not completely understood, psychological distress may affect the treatment adherence behavior in patients with HF [52]. Poor adherence to treatment is associated with increased morbidity and mortality in patients with HF [53]. Clustered depression and anxiety can be a stronger predictive marker of the severity of the illness or poor prognosis than depression alone in hospitalized patients with HF. This cluster may also be an important marker for psychological distress, particularly in hospitalized patients with HF.

Study limitations

There were some limitations in this study. First, this was a single-center cohort study. The clinical characteristics of our patients might not reflect those of general cardiovascular patients with HF. Second, the patients admitted to our hospital were not consecutively enrolled in our main study. Many patients who received emergent or intensive care were not enrolled because they could not complete the questionnaires. Third, the questionnaires were not completed prior to discharge. The primary aim of our main study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of the hospital stay in our patients ranged from a few days to several months because the severity of HF or comorbidities was heterogeneous. For a long-term prognosis, the assessment just before discharge might be more appropriate. However, previous studies have demonstrated that depression at the time of hospitalization, not prior to discharge, is associated with a poorer prognosis in patients with cardiovascular disease [54–57]. Fourth, the number of subjects was relatively small. Therefore, subgroup analysis was not feasible.

Conclusions

Our results showed that clustered depression and anxiety were predictors of death from any cause or rehospitalization due to worsened HF and refractory arrhythmia in patients with HF. This cluster may be an important marker for poor outcomes in patients with HF.

Conflict of interest

None declared.

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