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Q33 急性期後入院中に，どのように経口薬を導入していくのか

回答：[redacted] 戸高浩司

point

- ●ACE I → +β遮断薬が基本だが，両者とも十分量を目指すことが大事．
- ●β遮断薬は start low and go slow．場合によっては start lower and go slower．
- ●いたずらに完全回復を待っての開始より，早めに退院前導入するのが重要．
- ●退院後の生活をイメージして用量を調節，外来でも増量は可能．
- ●患者さんは一人ひとり異なるので，型通りの導入法にこだわらず，状態をよく観察して，スケジュールの個別化が必要．

急性心不全および慢性心不全のそれぞれの治療・管理法については，ガイドライン[1,2]も整備され，ある程度確立しています．しかし，急性期ケア（注射薬中心）から慢性期ケア（経口薬中心）への移行に関しては，心不全には180°方向性が違う治療法が混在するなか，どのように行うかについての具体論は，記載がありません．症例ごとに心不全の原因，増悪因子，合併症などの差異が大きいことも，問題を複雑にしています．虚血性心疾患や，弁膜症，徐脈性不整脈など，非薬物療法が奏効する場合に，そちらを優先するのは当然ですが，症候群としての心不全は，心機能の低下を契機とした神経体液性代償機構の破綻・過誤による悪循環が病態の中心をなしており[3]，そこへの介入は，どの心不全にも共通します．また，心機能そのものの是正ができない重症心不全症例（拡張型心筋症，虚血性心筋症など）の治療の中核になります．したがって，以下の文章については，そのような症例が対象という前提で読んでください．移行期においてはevidenceのしっかりしていない部分も多く，以下には筆者，弊学の経験的な方法も記載しています．

Q β遮断薬とACE Iは，どちらを先に始めるほうがよいのでしょうか？

A 慢性期の薬物治療として，特別な事情がなければ，両者とも必要ということには異論がないものと思います．いずれの薬剤も少量から開始し，漸増するのにかなりの期間を要する（特にβ遮断薬）ために，投与する順番がしばしば問題となります．歴史的な背景から，ACE Iが先でβ遮断薬が後とされてきましたが，疑問が呈され，CIBIS Ⅲ[4]で直接の比較が試みられました．結果としては，いずれが先でも予後に大きな差はな

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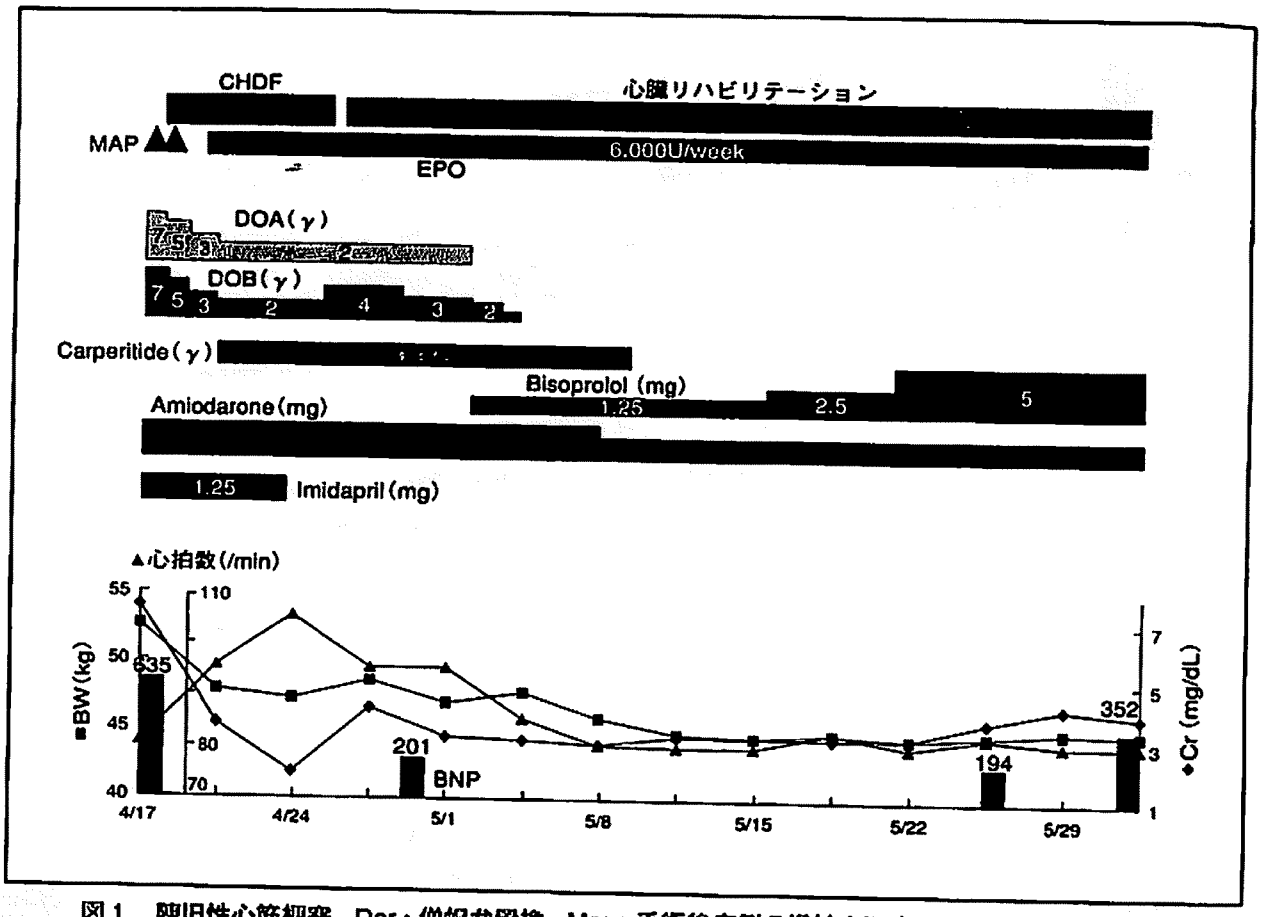


図1　陳旧性心筋梗塞，Dor・僧帽弁置換・Maze手術後症例の慢性心不全急性増悪後の治療経過
DOA：ドパミン，DOB：ドブタミン，CHDF：持続的血液濾過透析，MAP：濃厚赤血球，
EPO：エリスロポイエチン，BW：体重，Cr：血清クレアチニン

く．先に開始した薬剤が目標量に達する率が高い，というものでした．β遮断薬が先のほうが1年目の突然死が少ないというサブ解析も出されましたが，この試験は約半年もの間，いずれかの薬剤が投与されないという，かなり極端な設定がされていることに注意しなければいけません．心不全の年間死亡率を考えれば，そう悠長に構えている余裕はないはずです．

実際にはACEIの効果発現が早く，β遮断薬のように一時的悪化懸念がないため，先に投与されることがほとんどです．我々は，ACEIがある程度まで（エナラプリル2.5〜5 mgなど）増量された時点で，β遮断薬を導入開始しています．これには，一定量以上のACEIでは，用量反応性がそれほど強固ではないという事実も参考にしています[5]．その後は症状，血圧，心拍数，体重，腎機能，血清Kなどの反応をみながら，原則，交互に増量を試みるようにしています．実際には心房細動，腎機能障害の有無などにより，反応性，認容性が症例ごとに異なり，いずれかを優先する・せざるを得ないことも多くあります．

図1の例は，ACEIを諦めβ遮断薬を開始した症例です．OMIに対してDor＋MVR＋Maze手術をされていた70歳代女性で，数年後に繰返す心房頻拍をきっかけに心不全が増悪し，カテコラミン依存の状態で前医より転院となりました．β遮断薬は中止してありました．元々慢性腎不全を伴っており，利尿が

つかないため，CHDF施行．少量投与されていたイミダプリルを中止し，代わりにカルペリチドにてRAAS抑制を期待しました．カテコラミン漸減後にアミオダロンで抑えきれていない心房頻拍のrate controlも期待して，ビソプロロールを導入しています．EF 30%程度と比較的心機能が良かったため，速いペースで増量できています．その結果，心拍数はよくコントロールされ，回復後に何度かACE Iのごく少量を試験投与してみましたが，sCrが3 mg/dL強（Ccr 10 mL/min程度）で毎回乏尿となるため，断念しました．心リハも含めた集学的治療により，軽快退院されています（後日再入院の上心筋焼灼術を施行）．

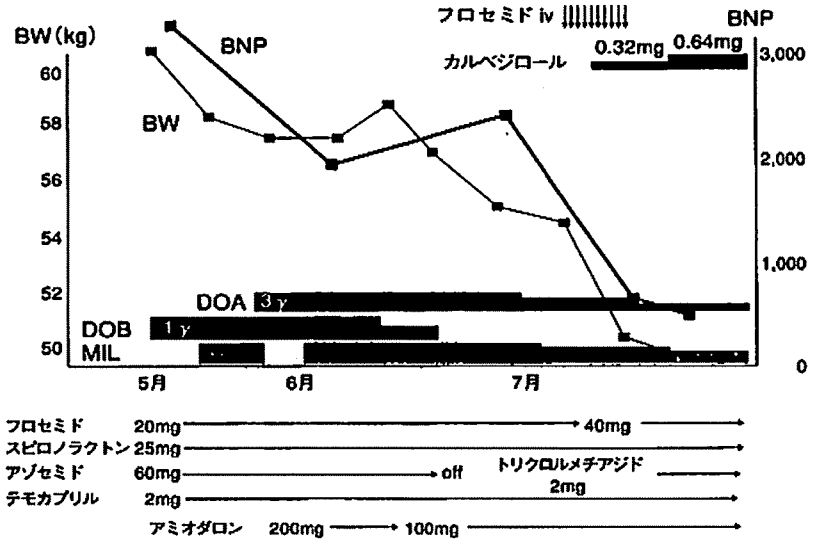
心不全という病態を考えた場合，2系統の主たる代償機能の誤りを，できるだけ早く正してやることが，予後改善には肝要です．したがって「どちらを先に？」という問いが，いずれを優先して抑えたほうがよいかという背景でなされているのであれば，その答えは症例ごとに異なります．ESCガイドライン[1]には（大規模研究の結果に忠実であれば），β遮断薬は一律にACE Iが十分量投与されてから開始するように記載されていますが，上記症例のように，いずれかが目標用量に達していなくても，他方の薬剤導入を遅らせるべきではありません[2]．

Q 血圧が低いのですが，ACE I・β遮断薬を使えますか？

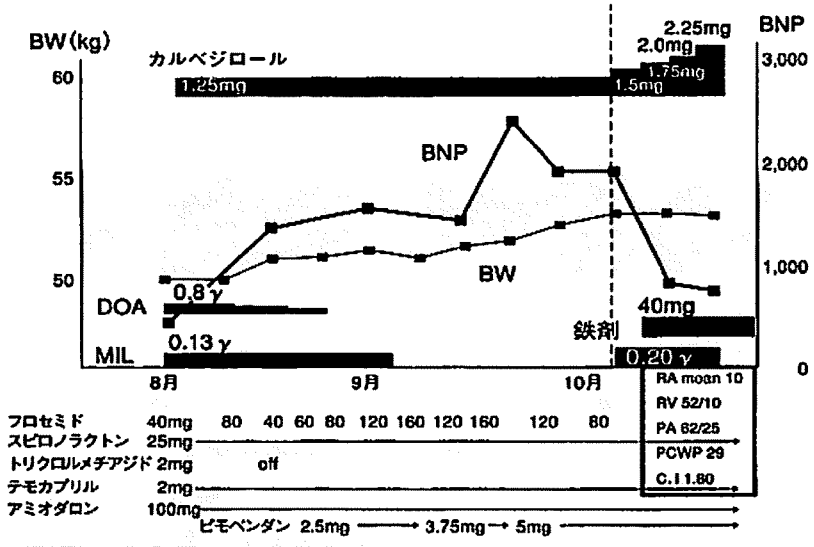
A 高血圧性心疾患に伴う心不全などを除いて，重症心不全の症例は血圧が低いことが多いです．どのくらい血圧が低いとこれらの薬が投与できないかについて，明確な数値的基準はありません．AHAガイドライン[2]にも，特定の血圧値をもって治療すべき低血圧と判断すべきではないと記載されています．症候性の低血圧や末梢循環不全を伴っている場合には禁忌であると思いますが，目安として，収縮期血圧が90～85 mmHg未満では投与をためらうというのが一般的ではないでしょうか．しかしながら，重症で長期にわたる心不全症例では，非常に少量から慎重に開始すれば投与可能である場合があるため，一概に，血圧の数字のみをもって諦めるべきではありません．start low and go slowという格言を，β遮断薬のみならずACE Iにも当てはめてください．中期的には，心拍出量の増加に伴っていったん低下した血圧が上昇してくることも，よく経験します．変動の大きい血圧値のみに頼るのではなく，立ちくらみなどの症状や，尿量の変化，腎機能悪化の徴候に注意をはらって，一時的減量や，ACE Iとβ遮断薬の投与時間をずらすなどの工夫をすべきです．ただ，収縮期血圧が80 mmHg未満では，末梢循環不全（小さい脈圧，低Na血症などを伴う）が顕著である場合も多く，経験の豊富でない施設では投与しないほうが無難でしょう．

臨床所見から血圧が低い原因が明らかでない（≒治療抵抗性である）場合は，ワンポイントでスワンガンツをしてみるというやり方もあります．Subset Ⅲにある場合は利尿薬を緩めたり，Ⅰであれば何らかの異常な血管拡張を検索したほうがよいかもしれません．Ⅳの右下にあるのであれば強心薬が必要であり，ACE Iのごく少量から開始してみて，状態が改善してからβ遮断薬を考慮する

a）拡張型心筋症症例の慢性心不全急性増悪後の治療経過



b）同じ症例のβ遮断薬増量困難とスワンガンツデータ



c）導入成功後の経過と退院前のスワンガンツデータ

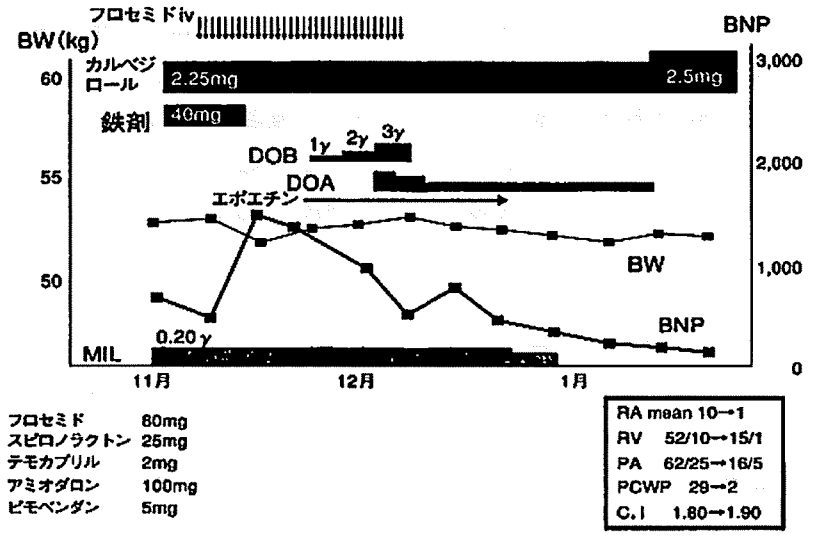


図2　拡張型心筋症の症例（60歳代女性）　MIL：ミルリノン

といった，ある程度の見切りが可能になります．また，右心系と左心系のバランス，LOS（低心拍出症候群）の原因についての重要な情報も得られ，前負荷をどの程度にコントロールするかが変わってきます．図2は，拡張型心筋症の60歳代女性症例が急性増悪で入院した時の治療経過ですが，a）でカテコラミンなどを漸減後に，前医で未導入であったカルベジロールを導入したものの，b）で体重，BNPの再上昇にみられるように，経過が思わしくありませんでした．この頃の収縮期血圧は70～80 mmHg台でした．そこで現状評価のために，b）の点線の時点でスワンガンツを挿入し，太枠内の結果を得ています．Subset Ⅳであり，強心薬なしでは無理と判断し，PDE Iを再開しています．

腎動脈や脳動脈に狭窄がある症例，脳梗塞の既往がある症例などは，血圧に特別の注意が必要であり，上記の原則は当てはまらず，慢性心不全の治療を緩めざるを得ないこともあります．

観察研究ではありますが，薬物治療を受けている心不全患者の予後は，収縮期血圧が低いほど悪いため[6]，利尿薬を最低限にする，必要のない硝酸薬を中止するなど，長期的には収縮期血圧が100 mmHgを超えるように努力すべきと思われます．

Q どの時点からβ遮断薬を開始すればよいのでしょうか？

A 教科書的には うっ血が取れて，静注強心薬が不要になった安定した時期に開始すべきであるとされています[1-2]．また，IMPACT-HF[7]で示されているように，退院前開始が予後改善のためには望ましいとされています．しかし，重症の心不全ではなかなか強心薬が切れない・漸減にかなりの時間がかかっている症例を，しばしば経験します．ACE Iは先に導入したものの，カテコラミンを減量しては増悪するため，なかなか中止できず，β遮断薬が開始できないような症例です．このような場合，カテコラミンが完全に切れるのを待ってβ遮断薬を開始しようとすると，導入に失敗したり，その後のup-titrationに非常に時間がかかったりします．そこで，強心薬（望むらくはPDE I）を少量投与しながら，微量のβ遮断薬（カルベジロール0.32 mg，≒1.25 mg錠の1/4など）を経験的に開始することがあります（図2a）．このような，ごく少量のβ遮断薬，強心薬との併用に意味があるか，科学的には証明されていませんが，このようなやり方でβ遮断薬に体を「慣らす」ことによって，初めて導入可能で，結果的には時間が節約できる症例があるのも事実です．start lower and go slowerとよばれる方法の一種でもあります．このまま強心薬を減量中止可能となった後に，β遮断薬を増量して悪化をみた場合は（利尿薬が増量可能ならそうしますが，LOSの場合などは），ピモベンダンを併用して維持するか，あるいは図2b，cのように，PDE Iを一時的に再開してまでもβ遮断薬のup-titrationを行うことで，最終的な導入，退院に成功することもあります．このような症例は稀ですが，そこまでしてβ遮断薬を導入するという，主治医側の強い意思があるか，「β遮断薬に認容性がなかった」で諦められたかでは，予後に大きな差が生じます．

Q β遮断薬は，入院中にどのくらいまで増量したらよいでしょうか？

A 目標用量（カルベジロールであれば20 mg/day，民族差がないとすれば もっと高用量まで）を目指すべきですが，入院にこだわる必要はありません．我々は，カルベジロール5 mgの達成を一応の目安としています．入院中に5 mgより低い用量で足踏みする症例については，BNPが少なくとも250～350 pg/mL[8]を切っていることなどの条件を満たせば，患者さんに退院後悪化の可能性と対処法を十分に説明して退院していただき，外来でgo slower（時間をかける）を実践することも しばしばあります．徐脈などにより増量が制限されることがありますが，十分なβ遮断を行うのが目的であり，闇雲に目標用量を目指すのではなく，個別の反応を考慮しなければなりません[9]．β遮断薬の用量ではなく，結果としての心拍数低下と予後が相関するというデータもあります．

また，本邦においては，MUCHA試験[10]で5 mg群と20 mg群に大差がなかったため，目標用量についても明確ではありません．直接検証しているJ-CHFの結果が，2009年のAHAで発表されました．2.5 mg群，5 mg群，20 mg群の予後に有意差はありませんでしたが，同等性を証明するにはパワー不足であり，低用量で十分という結論にはなりませんでした．

Q どの薬剤（RAAS系抑制薬，β遮断薬などの種類）がよいでしょうか？

A どの疾患領域にも共通しますが，基本的にevidenceをもつ薬剤を使用すべきです．本邦では保険上，RAAS系抑制薬ならエナラプリル，リシノプリル，カンデサルタン，スピロノラクトンにしか，心不全の適応がありません．適応外ですがevidenceをもっているRAAS系抑制薬では，他にカプトプリル，トランドラプリル，キナプリル，バルサルタンが処方可能です．ARBは，空咳が出ない以外は心不全の治療でACE Iを凌駕するような点はありませんので，あえて第一選択にする必要はないと思います．ACE IにARBを上乗せする効果に関しては，割愛します．ACE Iの中では，胆汁排泄性がどの程度あるかで多少の使い分けがありますが，基本的にはclass effect（異論もあり）と考えられており，明確な差はないと思います．レニン阻害薬については，これからの研究が待たれます．

アルドステロン阻害薬については，ループ利尿薬と併用されることが多く，高K血症でもないかぎり，投与に迷うことは あまりありません．女性化乳房等の副作用が問題となる場合は，選択的阻害薬が有用ですが，心不全そのものに対する効果に差異はないと考えられます．

β遮断薬については事情が異なり，カルベジロール以外に，本邦ではビソプロロールしか心不全に投与可能な薬剤は入手できません．メトプロロールについては，本邦で上市されている酒石酸塩の徐放錠と，海外で心不全に多くのevidenceのあるコハク酸塩徐放錠とは，薬物動態などに大きな差異があり，同じものではありません．β選択性，ISA，

inverse agonism など特性が細かく異なり，例えばbucindololで有用性が証明されなかったように，これらは重要な差異であると考えられます．したがって，はっきりしたevidenceのある薬剤以外は，使用すべきではありません．カルベジロールとビソプロロールについては，前者がinverse agonismが小さく導入がしやすい，ドブタミン使用時の強心作用がかなり減弱する，後者はHRへの影響が大きい，という若干の使い分けがあります．α遮断の有無により，ビソプロロールのほうが血圧低下が小さいように期待されますが，臨床的には実感できるほどの大きな差ではないように思います．カルベジロールの抗酸化作用がより有用であるとの期待も，推測の域を出ません．β遮断薬でカルベジロールのみが本邦では心不全に適応をもっているのは，ご存知の通りです．

最後に，きちんと治験をして適応を取得した製薬会社や研究者，協力頂いた患者さんたちの労に報いるためにも，evidenceのある薬剤〔＝保険適応のある薬剤となるような医療行政を期待(メモ)〕を選択すべきであるのは，別の意味で重要です．

メモ

●「適応外使用に係る医療用医薬品の取扱いについて」（通称「二課長通知」）の内容抜粋

国内で既に承認を受けている医薬品であって，
・承認を受けている効能・効果以外の効能・効果を目的とした医療，または
・承認を受けている用法・用量以外の用法・用量を用いた医療における使用
（＝「適応外使用」）が行なわれているものについて

1．適応外の効能・効果による使用について，関係学会等から要望があり，使用が必要とされ，健康政策局研究開発振興課から要請があった場合には臨床試験実施及びその成績等に基づく，一部変更承認申請を考慮する．
2．次の場合に，適応外の効能・効果等が，資料に基づいて医学薬学上公知と認められる場合には，臨床試験の全部又は一部を新たに実施することなく，資料に基づく承認の可否の判断が可能なことがあるので，医薬安全局審査管理課に相談されたい．
(1)外国（本邦と同等水準の医薬品承認制度を有する国）で当該効能・効果が承認され，相当の使用実績があり，その審査当局への承認申請資料が入手できる場合
(2)外国で当該効能・効果が承認され，使用実績，信頼できる論文がある場合
(3)公的研究等による信頼できる臨床試験の成績がある場合

この二課長通知が十分に機能していれば「evidence＝保険適応」となるはずであるが，必ずしもなっていない．

Q 経口強心薬は禁忌ですか？

A ジギタリス製剤を除いて，一般的には長期投与すべきでないと考えられます．ミルリノン経口やxamoterolの臨床試験結果を見れば，本邦で処方可能なデノパミ

ン，ドカルバミンなども長期投与すべきではないと考えられます．ただ，短期的に静注強心薬を用いずに，LOSなどの症状を取るためや，β遮断薬による一過性増悪に対処するために投与することは，是認されます．その際にも，ピモベンダンなど予後を悪化させないという試験成績がある薬剤を優先させるべきと考えられます．EPOCH[11]の結果からは，ピモベンダンについては，2.5 mg/dayであれば長期投与について，どうしても必要な症例に対して容認されると思われますが，催不整脈性も含めて長期安全性が確立してはいません．

ジギタリスについて，予後を悪化させないためには血中濃度を低く保つ必要があり，強心薬としての作用が発揮されていない用量なのかもしれません．

Q Ca拮抗薬は，良くないのでしょうか？

A ジルチアゼムは予後を悪化させる可能性が高く，ベラパミルも，少なくとも有用ではなかったため，避けるべきと思われます．アムロジピンなどの長時間作用型DHPは，予後に対し中立ですので，冠動脈攣縮合併例などには有用です．あくまで，ACEIとβ遮断薬を十分量投与することが先決であり，その後に，もし血圧に余裕があれば，別の目的で投与可能という位置づけになります．

[文　献]

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Atorvastatin Improves the Impaired Baroreflex Sensitivity via Anti-Oxidant Effect in the Rostral Ventrolateral Medulla of SHRSP

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We have demonstrated that oxidative stress in the rostral ventrolateral medulla (RVLM), a vasomotor center in brainstem, increases sympathetic nerve activity (SNA) and that oral administration of atorvastatin inhibited SNA via anti-oxidant effect in the RVLM of stroke-prone spontaneously hypertensive rats (SHRSPs). The impairment of baroreflex sensitivity (BRS) is known as the predictive factor of mortality in the hypertension and BRS is impaired in SHRSP. The aim of the present study was to determine whether oral administration of atorvastatin improved the impaired BRS via anti-oxidant effect in the RVLM in SHRSP. Atorvastatin (20 mg/kg/day) or vehicle was orally administered for 28 days in SHRSPs. Systolic blood pressure (SBP), heart rate, and 24-h urinary norepinephrine excretion as an indicator of SNA were comparable between atorvastatin- and control-SHRSP. Thiobarbituric acid-reactive substance (TBARS) levels as a marker of oxidative stress was significantly lower in atorvastatin-SHRSP than in control-SHRSP. Baroreflex sensitivity measured by the spontaneous sequence method was significantly higher in atorvastatin-SHRSP than in control-SHRSP. These results suggest that atorvastatin improves the impaired BRS in SHRSP via its anti-oxidant effect in the RVLM of SHRSP.

Keywords statin, oxidative stress, brain, hypertension, baroreflex

Introduction

Rostral ventrolateral medulla (RVLM) in the brainstem is the vasomotor center that determines basal sympathetic nerve activity, and the functional integrity of the RVLM is essential for the maintenance of basal vasomotor tone (1–3). We have demonstrated that oxidative stress in the RVLM increases the sympathetic nerve activity (4), and that nitric oxide (NO) in the RVLM decreases the sympathetic nerve activity (5,6). Previously, we also demonstrated that overexpression of endothelial NO synthase in the RVLM of Stroke-prone

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spontaneously hypertensive rats (SHRSPs) improved the baroreflex control of heart rate due to the sympatho-inhibition caused by the increase in NO production in the RVLM (7). However, it has not been determined whether the inhibition of oxidative stress in the RVLM improves the impaired baroreflex control of the heart rate of SHRSP or not.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are potent inhibitors of cholesterol biosynthesis, and statins have reported to have an anti-oxidant effect (8). Previously, we have demonstrated that orally atorvastatin increases the expression of NO synthase in the brain of SHRSPs (9), and that NO in the RVLM improves the impaired baroreflex control of heart rate in SHRSPs (7). These results suggested that orally atorvastatin might have the potential to improve the baroreflex control of heart rate in SHRSPs. Moreover, orally atorvastatin also inhibited the sympathetic nerve activity through the decrease in oxidative stress in the RVLM of SHRSPs (10).

Therefore, the aim of the present study was to investigate the effect of oral-administered atorvastatin on the baroreflex control of heart rate through its anti-oxidative stress in the RVLM of SHRSPs.

Materials and Methods

Animals and General Procedures

Twelve-week-old male SHRSPs/Izm and Wistar-Kyoto (WKY) rats (280 to 340g; SLC Japan, Hamamatsu, Japan) were fed a standard rodent diet. Food and tap water were available *ad libitum* throughout the study. The rats were kept in a room maintained at a constant temperature and humidity under a 12-h light period between 8:00 AM and 8:00 PM. After adaptation to these conditions over at least 2 weeks, SHRSPs were divided into two groups: 1) atorvastatin-treated SHRSP, treated with atorvastatin of 20mg/kg/day for 28 days, and 2) control-SHRSPs, treated with vehicle (0.5% methyl cellulose). All drugs were dissolved in 0.5% methyl cellulose and administered by gastric gavage everyday. Systolic blood pressure (SBP) and heart rate were measured using the tail-cuff method (BP-98A; Softron, Tokyo, Japan). We calculated the urinary norepinephrine excretion for 24 h as an indicator of sympathetic nerve activity, as described previously (4–7,10). To obtain the RVLM tissues, the rats were deeply anesthetized with sodium pentobarbital (100 mg/kg IP) and perfused transcardially with phosphate buffer saline (PBS) (150 mol/L NaCl, 3 mmol/L KCl, and 5 nmol/L phosphate; pH 7.4, 4°C). The brains were removed quickly, and sections 1 mm thick were obtained with a cryostat at –7 ± 1°C. The RVLM was defined according to a rat brain atlas as described previously (4–7,10), and obtained by a punch-out technique. This study was reviewed and approved by the committee on ethics of Animal Experiments, Kyushu University Graduate School of Medical Sciences, and conducted according to the Guidelines for Animal Experiments of Kyushu University.

Measurement of TBARS

The RVLM tissues were homogenized in 1.15% KCl (pH 7.4) and 0.4% sodium dodecyl sulfate, 7.5% acetic acid adjusted to pH 3.5 with NaOH. Thiobarbituric acid (0.3%) was added to the homogenate. The mixture was maintained at 5°C for 60 minutes, followed by heating to 100°C for 60 minutes. After cooling, the mixture was extracted with distilled water and *n*-butanolpyridine (15:1) and centrifuged at 1600 *g* for 10 minutes. The absorbance of the organic phase was measured at 532 nm. The amount of thiobarbituric acid-reactive substances (TBARS) was determined by absorbance, as described previously (4,10).

Measurement of Baroreflex Sensitivity by Spontaneous Sequence Method

Rats were initially anesthetized with sodium pentobarbital (50 mg/kg IP followed by 20 mg · kg^{-1} · h^{-1} IV). A catheter was inserted into the femoral artery to record arterial blood pressure, and a heart rate (HR) was derived from the blood pressure recording. The other catheter was also inserted into the femoral vein to allow for intravenous infusion of sodium pentobarbital. A tracheal cannula was connected to a ventilator, and the rats were artificially ventilated. Sequence analysis detected sequences of three or more beats in which there was an increase both in SBP and pulse interval (up sequence) or a decrease both in SBP and pulse interval (down sequence). Baroreflex sensitivity (BRS) was estimated as the mean slope of the up sequences (up BRS), the down sequences (down BRS), and also the mean slope of all sequences (sequence BRS) (11,12).

Statistical Analysis

All values are expressed as mean ± SEM. Comparisons between any two mean values were performed using Bonferroni's correction for multiple comparisons. ANOVA was used to compare the blood pressure, HR, baroreflex sensitivity, and TBARS level in atorvastatin- or control-SHRSP and WKY. Differences were considered to be statistically significant at a P value of < 0.05.

Results

BP, HR, and Urinary Norepinephrine Excretion

Systolic blood pressure was significantly higher in atorvastatin-SHRSP and control-SHRSP than in WKY, and atorvastatin did not alter SBP in SHRSP (Figure 1A). Heart rate was significantly higher in atorvastatin-SHRSP and control-SHRSP than in WKY, and atorvastatin also did not alter HR in SHRSP (Figure 1B). Urinary norepinephrine excretion was significantly higher in atorvastatin- and control-SHRSP than in WKY, and was not different between control- and atorvastatin-SHRSP (Figure 2).

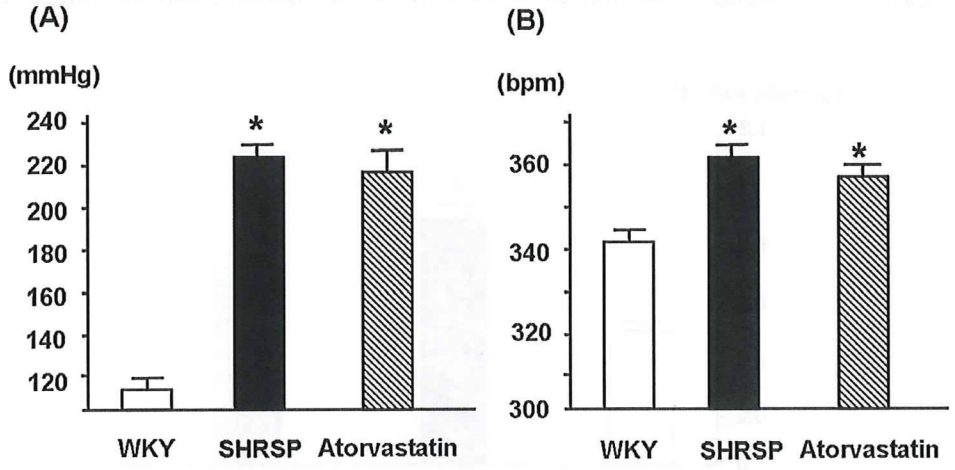

Figure 1. (A) Effects of the treatment with atorvastatin for 28 days on systolic blood pressure (SBP) of SHRSP and WKY. Data are shown as mean ± SEM (n = 5 for each group). *P < 0.05 vs. WKY. (B) Effects of the treatment with atorvastatin for 28 days on heart rate of SHRSP and WKY. Data are shown as mean ± SEM (n = 5 for each group). *P < 0.05 vs. WKY.

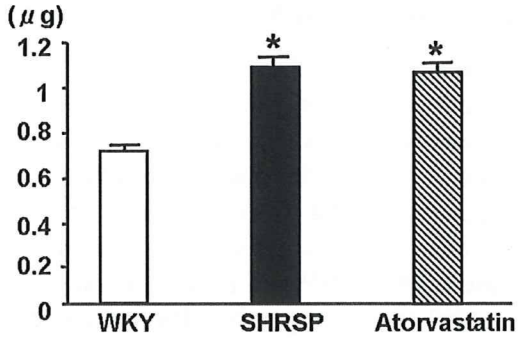

Figure 2. Effects of the treatment with atorvastatin for 28 days on 24-h urinary norepinephrine excretion of SHRSP and WKY. Data are shown as mean ± SEM (n = 5 for each group). *P < 0.05 vs. WKY.

TBARS Levels in the RVLM Tissues

Thiobarbituric acid-reactive substance levels in the RVLM were significantly higher in control- and atorvastatin-SHRSP than in WKY, and those of atorvastatin-SHRSP were significantly lower than those of control-SHRSP (0.70 ± 0.05 μmol/g wet wt vs. 0.91 ± 0.06 μmol/g wet wt, n = 5 for each, $P < 0.05$; Figure 3).

Baroreflex Sensitivity

Baroreflex sensitivity of control-SHRSP was significantly lower than that of WKY (9.2 ± 0.7 ms/mmHg vs. 19.1 ± 0.5 ms/mmHg, n = 5 for each, $P < 0.01$), and that of atorvastatin-SHRSP was significantly higher than that of control-SHRSP (14.8 ± 0.7 ms/mmHg vs. 9.2 ± 0.7 ms/mmHg, n = 5 for each, $P < 0.01$) (Figure 4).

Discussion

In the present study, we demonstrated for the first time that oral administration of atorvastatin improved the impaired baroreflex control of HR in SHRSP, and the improvement

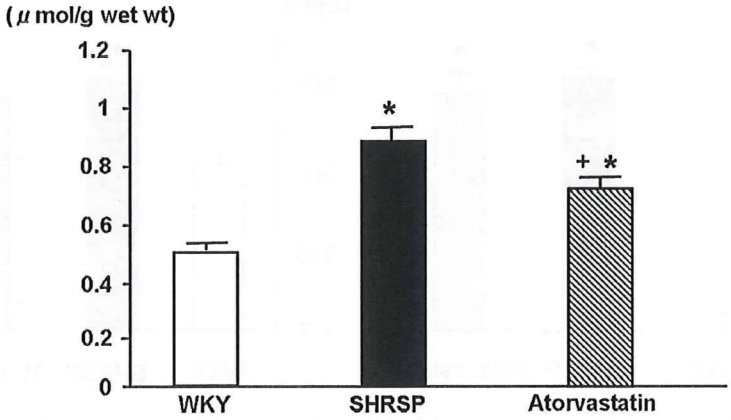

Figure 3. Effects of the treatment with atorvastatin for 28 days on TBARS levels in the RVLM of SHRSP and WKY. Data are shown as mean ± SEM (n = 5 for each group). *P < 0.05 vs. WKY; $^{+}$P < 0.05 vs. control-SHRSP.

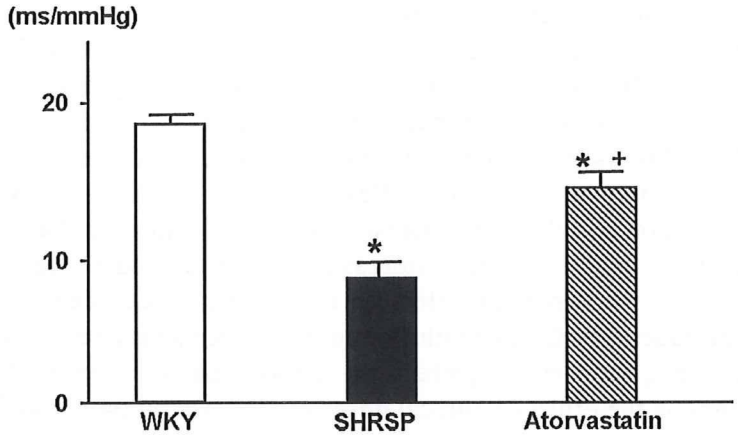

Figure 4. Effects of the treatment with atorvastatin for 28 days on baroreflex control of heart rate of SHRSP and WKY. Data are shown as mean ± SEM (n = 5 for each group). *P < 0.05 vs. WKY; $^{+}$P < 0.05 vs. control-SHRSP.

might be due in part to the inhibition of oxidative stress in the RVLM. Moreover, the improvement of baroreflex control of HR was independent of sympathetic nerve activity or blood pressure. We consider that these effects of atorvastatin benefit the treatment of the cardiovascular diseases with the disorder of baroreflex control.

In the present study, we demonstrated that atorvastatin improved the impaired baroreflex control without the reduction of BP or sympathetic nerve activity. Previously we reported that high-dose orally atorvastatin decreased BP and sympathetic nerve activity through the inhibition of oxidative stress in the RVLM (10). However, in the present study, low-dose atorvastatin did not decrease BP or sympathetic nerve activity, whereas oxidative stress in the RVLM was inhibited. We consider that this discrepancy is due to the smaller reduction of oxidative stress in the RVLM measure by TBARS compared to our previous study (10). We selected the lower dose of atorvastatin, because the effect of atorvastatin on baroreflex control should be examined in the condition excluded by BP and sympathetic nerve activity lowering effects. Moreover, baroreflex control is one of the key mechanisms responsible for the short-term control of BP. Impairment of this reflex has been found in a number of conditions, such as aging (13), heart failure (14), post-myocardial infarction (15), and the impairment of baroreflex sensitivity is known as the predictive factor of mortality in the hypertension (16). From the results in the present study, we consider that atorvastatin benefits the treatment for cardiovascular diseases.

The mechanisms in which atorvastatin improved the baroreflex control have not been determined in the present study. We consider that one of the possibilities in the mechanisms was the inhibition of oxidative stress in the RVLM, because the oxidative stress is the important modulator on the sympathetic nerve activity (4,10). Moreover, NO in the RVLM of SHRSPs improved the baroreflex control of HR (7). The inhibition of oxidative stress due to atorvastatin will contribute to the increase in NO in the RVLM of SHRSP and to the improvement of baroreflex control of HR.

A recent study suggests that the reduction of BP by clinical doses of statin is small but significant (17). However, the change in BP in the previous clinical study is significantly smaller than that in the present and previous animal study (10). Moreover, we are not able to determine the oxidative stress in the brain of human *in vivo* now and to determine whether the clinical doses of atorvastatin have the anti-oxidant effect in the

brain of the hypertensive patients. However, in the present study, oxidative stress in the RVLM is significantly reduced and baroreflex sensitivity is significantly improved by atorvastatin, whereas BP and sympathetic nerve activity are not altered. These results suggest that oxidative stress is inhibited and baroreflex sensitivity is improved by atorvastatin whose dose is insufficient for the reduction of blood pressure or sympathetic nerve activity. The improvement of baroreflex sensitivity could not be explained by the effect of atorvastatin on peripheral mechanisms, and we consider that baroreflex sensitivity is improved by the central action of atorvastatin. Clinical studies suggest that clinical doses of statins have the beneficial effect on arrhythmic sudden death and ventricular arrhythmia in the patients with heart failure, and these effects may be due to the improvement of the imbalance between sympathetic and parasympathetic nerve activity (18). It is necessary to examine the effect of clinical doses of atorvastatin on baroreflex sensitivity in a clinical study.

There are some limitations in the present study. First, we measured TBARS levels as the parameter of oxidative stress in the brain. Thiobarbituric acid-reactive substance levels are an indirect marker of oxidative stress, and there are other methods to measure oxidative stress. However, we previously measured oxidative stress directly in the brain of SHRSP and WKY using electron spin resonance spectroscopy and confirmed that TBARS levels are comparable to the levels of oxidative stress measured by electron spin resonance spectroscopy in the brain (4). The results suggest that TBARS levels are a valid parameter of oxidative stress in the brain. Second, we did not examine the TBARS levels in other areas of the brain, such as caudal ventrolateral medulla, nucleus tractus solitarii, paraventricular nucleus, cortex, hypothalamus, and cerebellum. We consider that these effects of atorvastatin was not unique in the RVLM, and we did not exclude the possibility that atorvastatin influences those areas thereby improving baroreflex control of HR in the present study. However, RVLM is the vasomotor center, and the integrated various inputs from other regions to RVLM influence the sympathetic outflow (1–3). Although it would be interesting to examine these parameters in other regions of the brain, we targeted the changes of oxidative stress in the RVLM due to atorvastatin in the present study.

Conclusions

Our results suggest that oral administration of atorvastatin improved the baroreflex control of heart rate due to the inhibition of oxidative stress in the RVLM of SHRSP.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Bionic Autonomic Neuromodulation Revolutionizes Cardiology in the 21st Century

Kenji Sunagawa, *Senior Member, IEEE*

Abstract — **In this invited session, we would like to address the impact of bionic neuromodulation on cardiovascular diseases. It has been well established that cardiovascular dysregulation plays major roles in the pathogenesis of cardiovascular diseases. This is the reason why most drugs currently used in cardiology have significant pharmacological effects on the cardiovascular regulatory system. Since the ultimate center for cardiovascular regulation is the brainstem, it is conceivable that autonomic neuromodulation would have significant impacts on cardiovascular diseases. On the basis of this framework, we first developed a bionic, neurally regulated artificial pacemaker. We then substituted the brainstem by CPU and developed a bionic artificial baroreflex system. We further developed a bionic brain that achieved better regulatory conditions than the native brainstem in order to improve survival in animal model with heart failure. We recently developed a bionic neuromodulation system to reduce infarction size following acute myocardial infarction. We believe that the bionic neuromodulation will inspire even more intricate applications in cardiology in the 21st century.**

I. OVERVIEW OF PREVIOUIS BIONIC STUDIES

In the human body, all cells, tissues, organs, and systems operate coherently. The presence of well-developed neurohormonal communications among these components of the body is the essential infrastructure that makes coherent functioning possible. If we could incorporate such communication mechanisms into artificial systems, they would function as if they are an integral part of the corresponding native physiological systems. We call such well-integrated artificial systems bionic systems.

The bread-and-butter technology that is common to all bionic systems is the technique for interfacing with the native systems, in particular, the human body's regulatory systems. Unification of an artificial system with a native system requires bidirectional communications. In 1995, we developed one such system, a neurally regulated artificial pacemaker [1]. Physiological studies indicated that the instantaneous sinus rate was determined not only by the current sympathetic activity but also by the history of sympathetic activity. We quantified its history dependence by the impulse response of the sinus rate to sympathetic stimulation. Using the convolution integral of the impulse response with the instantaneous sympathetic activity, we could predict the precise sinus rate in real time [1].

The success of the neurally regulated bionic pacemaker has convinced us that the autonomic system can be effectively monitored and thereby manipulated by bionic systems. The clinical impact of direct manipulation of autonomic functions in cardiovascular diseases is very profound. The case of central baroreflex failure is an archetypal example of one such application. In treating this disease, it is conceivable that one can implement an artificial bionic baroreflex system as a kind of biological proxy capable of emulating the native central baroreflex function of the failing vasomotor center. The bionic baroreflex system consists of a pressure sensor (baroreceptor), microprocessor (vasomotor center) and nerve stimulator (for activation of sympathetic efferents). The system operates as an intelligent negative feedback regulator, and has been demonstrated in animals and patients to be effective in restoring normal baroreflex functioning [2-5].

Recently, we developed an artificial brain stem that takes over the native cardiac regulation, and optimized it to improve the survival of chronic heart failure [6]. Two weeks after the ligation of the left coronary artery in rats, surviving animals were randomized to vagal- and sham-stimulated groups. Vagal stimulation markedly improved the 140-day survival (86% versus 50%, P=0.008). The relative risk reduction of death reached over 70%. The success of the bionic treatment of heart failure opens up an entirely new therapeutic paradigm for patients with chronic heart failure.

II. BIONIC NEUROMODULATION IN ISCHEMIA

Although the bionic autonomic neuromodulation system prevented progression, thereby improved survival of chronic heart failure, it would be far desirable if we can prevent the development of heart failure. Ischemic heart disease has been known as one of the major causes of heart failure. Therefore, we examined whether bionic autonomic neuromodulation impacts ischemia-reperfusion injury of the heart. This particular application of bionic autonomic neuromodulation is critically important under clinical settings because early reperfusion of occluded coronary arteries has become a standard therapy worldwide.

Myocardial infarction has been known to augment sympathetic afferent traffic and reduce vagal efferent activity. We investigated whether short-term electrical stimulation of

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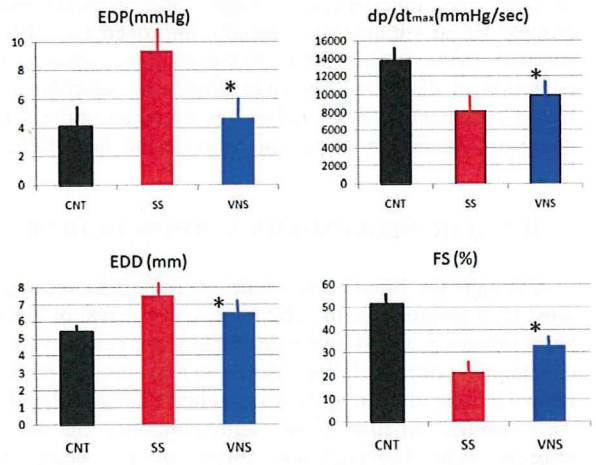
the vagal nerve could ameliorate cardiac dysfunction in a distant period after ischemia-reperfusion injury.

Ischemia-reperfusion injury model was created in Sprague-Dawley rats by ligating the left coronary artery for 30 min followed by reperfusion. We stimulated the right vagal nerve (the stimulation condition is proprietary) from the onset of ischemia for 3 hrs. We measured hemodynamics before ischemia, 4 days after ischemia with and without bionic autonomic neuromodulation. We estimated left ventricular function using echocardiography. We estimated infarction size histologically 4 days after ischemia.

III. RESULTS

As shown in the upper panels of figure, in comparison with sham stimulation (SS, n=6), vagal nerve stimulation (VNS, n=6) significantly decreased left ventricular end-diastolic pressure, and increased left ventricular (dp/dt)max suggesting improved left ventricular function. CNT represents the control condition (n=4). The improvement of left ventricular function was paralleled with decreased end-diastolic dimension (EDD), and increased shortening fraction (EF) as shown in the lower panels in the figure. Histological examination further supported the notion that vagal stimulation decreased the infarction size (33±5% vs. 24±3%, $p<.01$). Biochemical analysis indicated that vagal stimulation downregulated mRNA of procollagens, such as Col1a1, Col3a1, and Ctgf, in infarcted myocardium. Therefore, the positive impact of vagal nerve stimulation might have, at least in part, resulted from inhibition of collagen production in ischemia-reperfusion injury.



IV. DISCUSSION

We have shown that vagal stimulation early after the creation of ischemia resulted in marked reduction in infarction size and improvement of left ventricular function with attenuated cardiac remodeling. Although the effect of vagal nerve stimulation on long term survival remains to be investigated, it is conceivable that the vagal nerve stimulation early after ischemia-reperfusion injury may have a positive impact on such a hard endpoint.

The mechanism by which the bionic neuromodulation improves ischemia-reperfusion injury remains unknown. The bradycardiac effect of vagal stimulation might be a contributing factor. However, our pilot study indicated that a comparable heart rate reduction induced by beta-blocker failed to show the positive impacts on ischemia-reperfusion injury as much as the vagal stimulation did. Theretofore, mechanisms other than the bradycardiac effect such as energy sparing effect, anti-inflammatory effect and anti-oxidant effect need to be considered [7-10].

V. CONCLUSION

Vagal nerve stimulation reduces infarct size, improves left ventricular function and attenuates left ventricular remodeling after ischemia-reperfusion injury. Bionic autonomic neuromodulation should inspire even more intricate applications in cardiology in the 21st century.

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