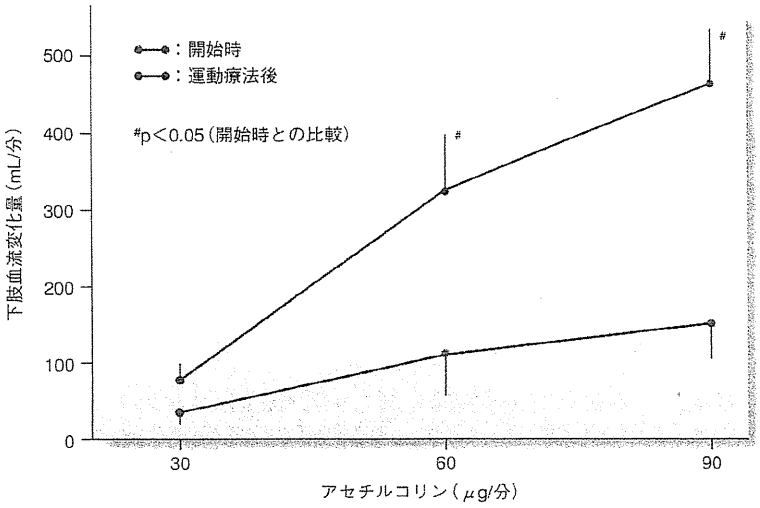

図2　アセチルコリン投与による下肢血流の変化（文献2より引用）
慢性心不全に対する6カ月間の運動療法により，アセチルコリン投与後の下肢血流変化量が著明に増加した。

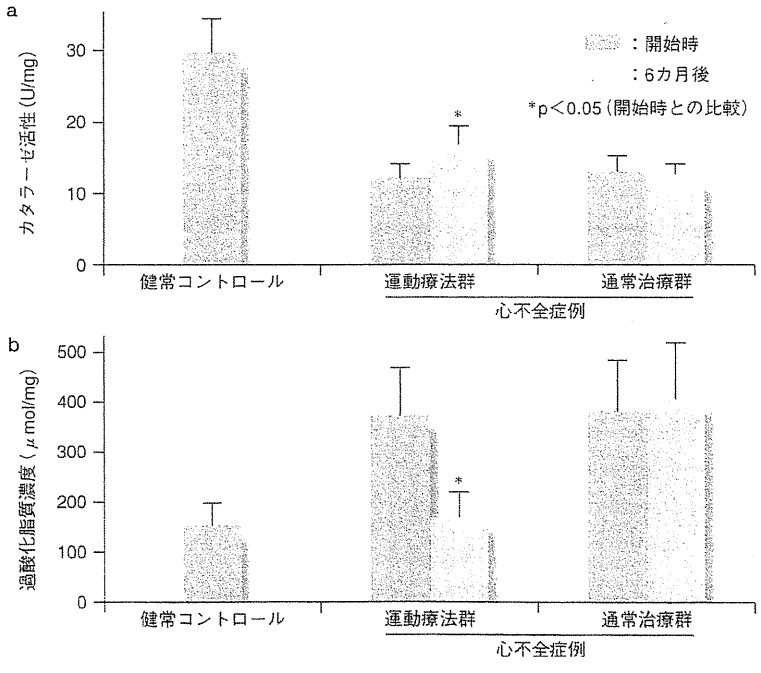

図3　大腿四頭筋外側広筋の抗酸化酵素カタラーゼ活性（a）および過酸化脂質濃度（b）
（文献17より引用）
慢性心不全の開始時に認められるカタラーゼ活性低下や過酸化脂質濃度上昇が，6カ月の運動療法により有意な改善を認めた。

作用[4]などが報告されている。

運動療法の末梢効果

慢性心不全の運動療法による運動耐容能改善作用の多くは，骨格筋や末梢血管などを介した末梢性機序によると考えられている。

(1) 骨格筋機能・血管内皮機能

慢性心不全では，骨格筋の慢性的低灌流と身体活動低下に基づくdeconditioningにより，血管内皮機能障害，毛細血管密度の減少，酸化酵素の多いslow twitch fiber Ⅰ型から解糖系酵素の多いfast twitch fiber Ⅱ型への筋線維型変換，ミトコンドリア密度の減少，抗酸化酵素活性の低下，炎症性サイトカインの増加などの変化が生じる。

運動療法は，血管内皮機能の改善による血流増加[2,14]（図2），骨格筋の代謝機能や形態の改善[15,16]，抗酸化酵素活性の改善（図3）[17]，腫瘍壊死因子（tumor necrosis factor；TNF）-α，interleukin（IL）-6などの炎症性サイトカインの低下（図4）[18]などの作用により，運動耐容能の改善に寄与することが報告されている。

(2) 自律神経

慢性心不全では，骨格筋などの末梢組織から交感神経中枢への求心性刺激が増加しており，交感神経活性の亢進は，血圧・心拍数増加による心筋酸素

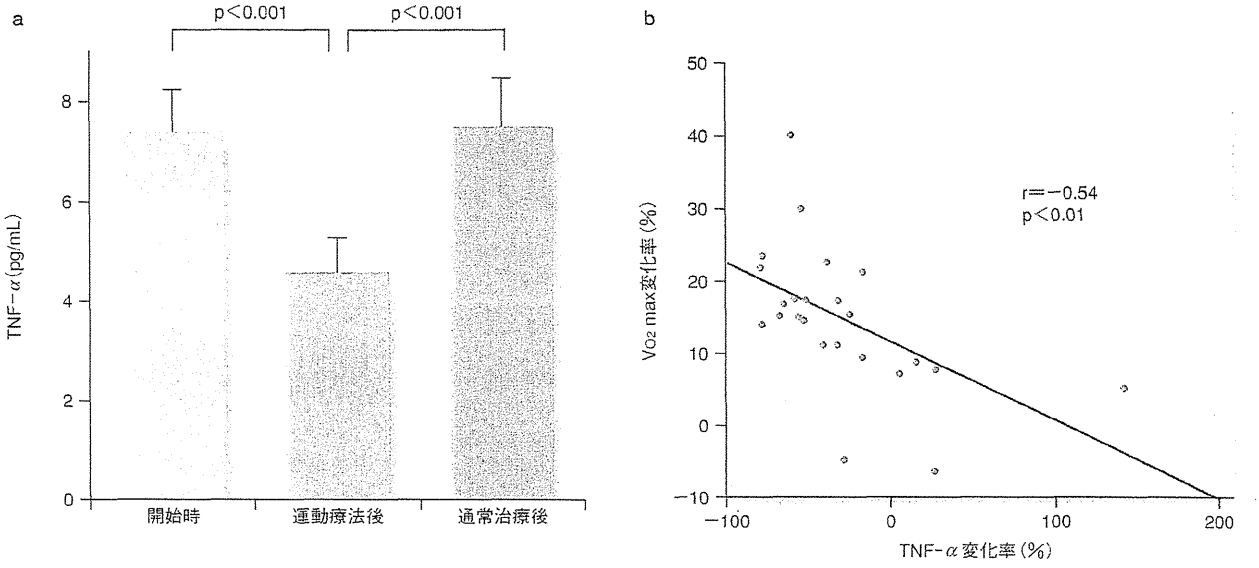

図4 慢性心不全における血中TNF-α濃度の変化(文献18より引用)
3カ月間の運動療法により，血中TNF-α濃度が有意に減少(a)し，その変化率は運動耐容能の変化率と有意な負の相関を認めた(b)。

消費量の増大，血小板機能の活性化，血管過収縮による後負荷の増大をもたらす。

運動療法の効果として，筋交感神経活動亢進の改善(図5)[19]，血中ノルアドレナリン濃度の減少[4]，副交感神経機能活性化による圧受容体反射感受性や心拍変動の改善[1]が報告されている。

(3)運動時換気効率

慢性心不全では，運動時の二酸化炭素排出量(V_{CO_2})増加に対する分時換気量(V_E)増加の比(V_E/V_{CO_2} slope)が重症度とともに上昇することが知られ(運動時換気亢進)，労作時息切れの主な原因となっている。機序として，換気血流不均等による生理学的死腔増大，呼吸中枢化学受容体のCO_2感受性亢進，骨格筋からの神経性反射(ergoreflex)亢進などが考えられている。

運動療法は，CO_2感受性の改善，ergoreflexの減少，呼吸筋機能の改善などを介して換気効率を改善[20]し，呼吸困難感を軽減する。

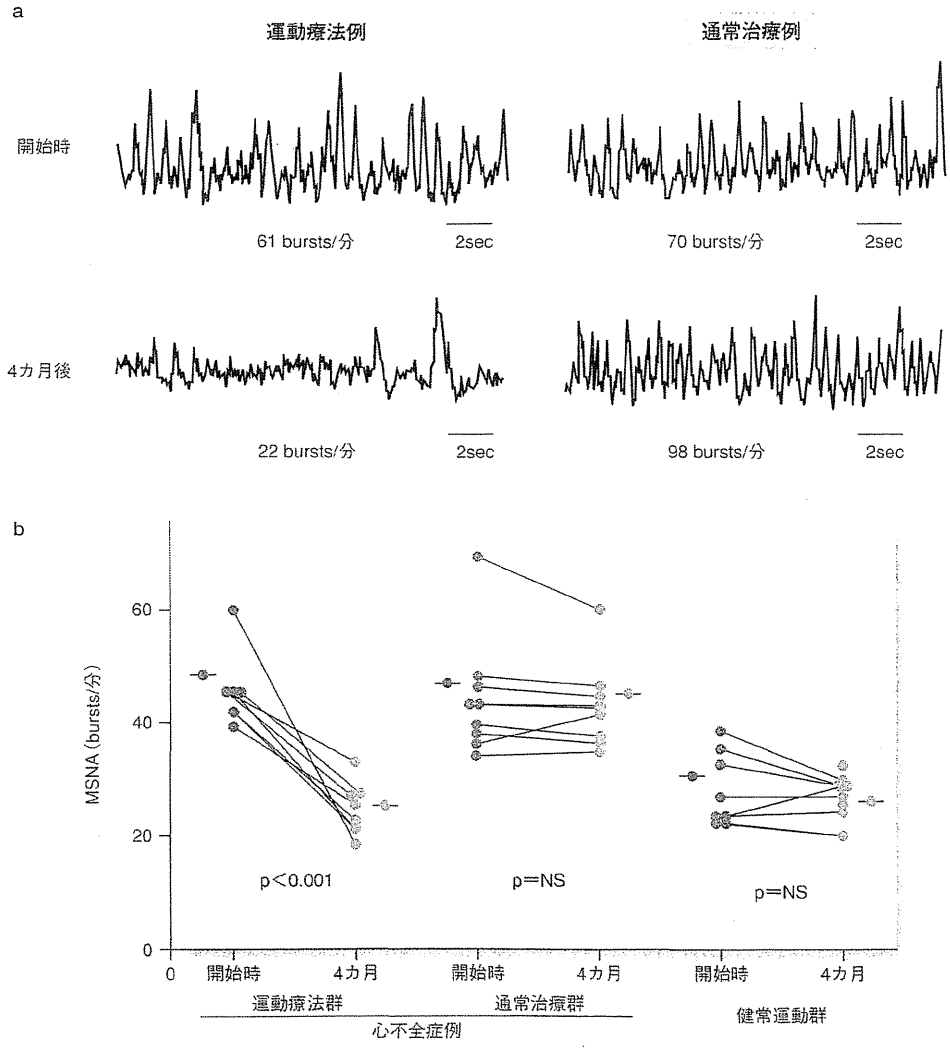

図5　慢性心不全における筋交感神経活動の変化
（文献19より引用）

a：運動療法群および通常治療群の代表例（上段；開始時、下段；4カ月後）、b：MSNA値（bursts/分）の変化。慢性心不全では4カ月の運動療法により、MSNAが健常者レベルまで有意に低下した。
MSNA：muscle sympathetic nerve activity（筋交感神経活動）

運動療法の実際

(1)適応と禁忌

慢性心不全で運動療法の適応となるのは，NYHAⅡ～Ⅲ度の体液量コントロールされた安定期症例，すなわち自覚症状や肺うっ血・浮腫の増悪を認めず，体液量が適正に管理され，運動療法の禁忌(表1)がない症例である。高齢者，高度低心機能例，補助人工心臓装着例，ICD/CRT植込み例などでも，適切な運動療法の安全性は確立しており禁忌とはならない。

表1　運動療法の禁忌

絶対的禁忌

①過去1週間以内に自覚症状(呼吸困難，易疲労感など)が増悪した心不全
②不安定狭心症または閾値の低い心筋虚血を認める例
③手術適応のある重症弁膜症，特に大動脈弁狭窄症
④重症の左室流出路狭窄(閉塞性肥大型心筋症)
⑤未治療の運動誘発性重症不整脈(心室細動，持続性心室頻拍)
⑥活動性の心筋炎
⑦急性全身性疾患または発熱
⑧運動療法が禁忌となるその他の疾患(中等症以上の大動脈瘤，重症高血圧，血栓性静脈炎，2週間以内の塞栓症，重篤な他臓器障害など)

相対的禁忌

①NYHA Ⅳ度または静注強心薬投与中の心不全
②過去1週間以内に体重が2kg以上増加した心不全
③運動により収縮期血圧が低下する例
④中等症の左室流出路狭窄
⑤運動誘発性の中等症不整脈(非持続性心室頻拍，頻脈性心房細動など)
⑥高度房室ブロック
⑦運動による自覚症状の悪化(疲労，めまい，発汗多量，呼吸困難など)

禁忌とならないもの

①高齢者
②高度左室機能低下例
③補助人工心臓(LVAS)装着例
④植込み型除細動器(ICD)・心臓再同期療法(CRT)植込み例

(2)基本事項

慢性心不全症例は原因疾患や重症度が多様であるため，開始時に問題点を十分確認し，臨床所見や運動負荷試験に基づいて決定した運動処方に従って個別に運動メニューを作成し，慎重に運動療法を実施する。原則として心電図モニターを装着した監視下での短時間低強度運動から開始し，自覚症状や身体所見を観察しながら徐々に時間と強度を増量し，安全性が確認されたのち非監視下在宅運動療法に移行する。

(3)開始初期

推奨される運動は，歩行，自転車エルゴメータなどの有酸素運動であり，短時間(5～10分間)・低強度(歩行50～70m/分あるいは自転車エルゴメータ10～20W)の運動を1日1～2回で開始する。頻度は，重症例で週3回，軽症例で週5回程度とする。問題がなければ，自覚症状や身体所見を目安にして1カ月程度かけて徐々に時間と強度を増量する。筋力低下が著しい症例ではレジスタンス運動も有効であり，ゴムベルトや軽いダンベルを使用した四肢筋の屈伸運動を15～20分間，週2～3回行う。

開始初期は運動量が過大でないか，自覚症状，体重，心拍数，BNP値などの変化に注意する。一時的に悪化傾向があっても多くの場合，運動量の一時的減量，水分制限や利尿薬の一時的増量で改善し，継続が可能である。

(4)運動処方

開始1～2週間ほどの運動に慣れてきた時点で，心肺運動負荷試験(cardiopulmonary exercise testing；CPX)を施行し，運動処方を行う。目標心拍数は，peak Vo_2の40～60%，あるいは嫌気性代謝閾値(anaerobic

threshold；AT)レベルで，監視下運動療法時の心拍数，自覚症状，心機能，BNP値なども参考にして決定する。CPXを実施していない施設では，症候限界性運動負荷試験で心拍数予備能の30～50%とする。

心房細動やペースメーカ調律など，目標心拍数の決定が困難な症例では，自覚的運動強度(Borg指数)6～20のうち11(楽である)～13(ややきつい)のレベルとする。運動時間は1日合計20～60分の範囲で，重症度により決定する。

(5)安定期から維持期へ

安定期になれば非監視下在宅運動療法に移行可能であるが，重症例では週1回程度の監視下運動療法との併用が望ましい。運動療法やβ遮断薬の効果で心拍数が次第に低下することが多いため，開始2～3カ月の時点で運動負荷試験を再検して運動処方を見直し，6カ月以降は維持期として在宅運動療法を継続する。再発予防に向けた教育として，体重や血圧を毎日測定するなどの自己管理を徹底させ，運動方法や生活習慣に修正すべき点があれば指導する。

まとめ

慢性心不全では，身体活動の低下や骨格筋への低灌流が骨格筋機能障害をもたらし，交感神経活性亢進・ergoreflex亢進から後負荷増大・運動時換気亢進によって，さらに心機能や症状を悪化させるという悪循環が形成されている(図6)。

運動療法は運動耐容能やQOLを改善させるだけでなく，骨格筋機能の改善によってこの悪循環を断ち，心不全入院を減少させ長期予後も改善させる可能性がある。しかし，慢性心不全

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症例が運動療法のアドヒアランスを長期間高く維持することの困難さは，大規模無作為割り付け試験HF-ACTIONの結果からも明らかである。近年，運動方法による効果の違い[21]やさまざまなレジスタンス運動の有効性[22]が報告されており，今後，有効性・安全性・アドヒアランスの点で，慢性心不全症例にとっての最適な運動プロトコールが明らかにされていくことが期待される。

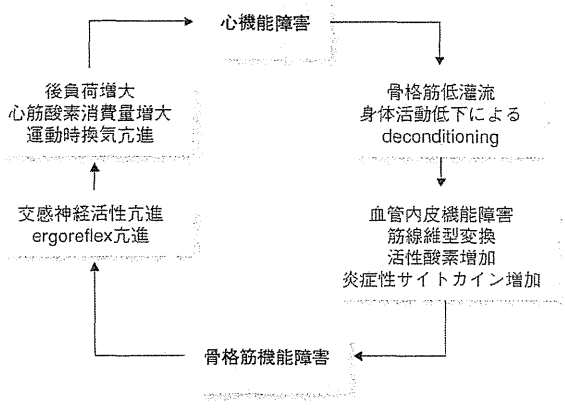

図6 慢性心不全における心機能障害と骨格筋機能障害の連関

thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 97: 553-561, 1998.
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MicroRNA 210 as a Biomarker for Congestive Heart Failure

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MicroRNAs (miRNAs) are endogenous small RNAs that are 18–23 nucleotides long. Recently, plasma miRNAs were reported to be sensitive and specific biomarkers of various pathological conditions. In the present study, we focused on miR-210, which is known to be induced by hypoxia and might therefore be an excellent biomarker for congestive heart failure. Plasma miR-210 levels and expression levels in mononuclear cells and skeletal muscles were elevated in Dahl salt-sensitive rats with heart failure. We also assessed miR-210 expression in patients with heart failure. The miR-210 expression levels in the mononuclear cells of patients with NYHA III and IV heart failure according to the New York Heart Association (NYHA) functional classification system were significantly higher than those with NYHA II heart failure and controls. Although no significant correlation was observed between plasma brain natriuretic peptide (BNP) and plasma miR-210 levels in patients with NYHA II heart failure, patients with an improved BNP profile at the subsequent hospital visit were classified in a subgroup of patients with low plasma miR-210 levels. Plasma miR-210 levels may reflect a mismatch between the pump function of the heart and oxygen demand in the peripheral tissues, and be a new biomarker for chronic heart failure in addition to plasma BNP concentrations.

Key words biomarker; heart failure; microRNA

MicroRNAs (miRNAs) are endogenous small RNAs, comprising approximately 18–23 nucleotides, which bind to the 3′-untranslated region of mRNAs of protein-coding genes to downregulate their expression.[1,2] miRNAs play an important role in various physiological and pathological processes.[3,4] So far, more than 1500 human miRNAs have been identified (http://www.mirbase.org). They are expressed in a tissue- or cell-specific manner.[5] Most human protein-coding genes are thought to be targeted by miRNAs[6,7] that appear to function as rheostats to fine tune protein output.[8,9]

Recently, miRNAs were reported to be present in various body fluids.[3,10,11] More than 90 types of miRNAs have been detected in human sera using next-generation sequencing.[10] Plasma miRNAs are embedded not only RNA-induced silencing complex (RISC) but also others, exosomes and/or microparticles.[12–14] We recently reported that the plasma concentrations of myocardium-specific miRNAs are excellent biomarkers of myocardial infarction.[12,14] Other groups also report that plasma miRNAs are sensitive and specific biomarkers of various tissue injuries and pathological conditions.[15–18]

The present study examined whether circulating miRNAs can be used as biomarkers in patients with heart failure. Recently, Tijsen *et al.* reported that circulating plasma miR-423-5p is most closely related to a clinical diagnosis of heart failure.[17] Moreover, we reported that the plasma concentration of miR-126 is negatively correlated with the severity of heart failure.[19]

In the present study, we determined whether miR-210 is a biomarker for congestive heart failure. Chronic heart failure is characterized by insufficient oxygen supply to the peripheral tissues; miR-210 is highly induced by hypoxia. MiR-210 has already attracted a great deal of attention as a biomarker for various diseases including breast cancer,[20] acute cerebral ischemia,[21] atherosclerosis obliterans,[22] and acute kidney injury.[23] Aberrantly accelerated proliferation and metabolism are typical characteristics of cancer cells, which lead to an imbalance between oxygen supply and consumption, causing hypoxia. Moreover, the obliteration of arteries or tissue injury exposes peripheral tissues to hypoxic conditions. In diseases with hypoxia, miR-210 might be a useful auxiliary biomarker (*i.e.*, not for primary diagnosis). It has been established that miR-210 is specifically induced by hypoxia-inducible factor 1α (HIF-1α) during hypoxia. In addition, miR-210 might repress iron–sulfur cluster assembly protein (ISCU), leading to the repression of mitochondrial respiration, reducing oxidative stress, which may protect cells from apoptosis.[24]

In the present study, miRNA array analysis revealed miR-210 is elevated in the plasma of rats with heart failure. We confirmed that miR-210 is upregulated by hypoxia in rat myocardial cells (H9c2) and tested the hypothesis that the expression level of miR-210 increases in the peripheral tissues of rats with heart failure. Finally, we examined the possibility of miR-210 as a biomarker for heart failure in human patients.

MATERIALS AND METHODS

Rat Heart Failure Model Dahl salt-sensitive rats fed a high-salt diet for 8 weeks showed a systolic blood pressure (SBP) exceeding 220 mmHg, markedly elevated plasma brain natriuretic peptide (BNP) levels, marked cardiac hypertrophy, and massive proteinuria and were, therefore, considered to have chronic heart failure condition in accordance with previous reports.[25–27] Male Dahl salt-sensitive rats (4 weeks old) were purchased from Japan SLC (Shizuoka, Japan). The rats were housed in a temperature-controlled room on a 12-h light/12-h dark cycle and fed low (control group: 0.03%) or

The authors declare no conflict of interest.

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high (heart failure group: 8%) salt rat diet (Oriental Yeast, Tokyo, Japan) and tap water *ad libitum*. Body weight and SBP were measured weekly. SBP was measured using the tail-cuff method (BP-98A: Softron, Tokyo, Japan). After 8 weeks of treatment, blood was collected from the inferior vena cava under pentobarbital anesthesia with ethylenediaminetetraacetic acid (EDTA) for RNA measurement and sodium citrate for BNP enzyme-linked immunosorbent assay (ELISA) as an anticoagulant. Plasma was isolated by centrifugation at 1600×***g*** for 15 min at 4°C. Mononuclear cells were isolated by Histopaque-1083 (Sigma-Aldrich, MO, U.S.A.) density gradient centrifugation. The cells were washed 3 times in phosphate-buffered saline (PBS). The heart, kidneys, and skeletal muscles (*i.e.*, the quadriceps femoris) were resected and immediately frozen in liquid nitrogen for transcriptome analysis or Western blot analysis.

The present study was conducted in accordance with the guidelines of the National Cerebral and Cardiovascular Center for the Care and Use of Experimental Animals and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Adequate measures were taken to minimize the animals' pain and discomfort.

Confirmation of miR-210 as One of the miRNAs Most Markedly Upregulated by Hypoxia H9c2 cells were obtained from the American Type Culture Collection (ATCC, MD, U.S.A.) and maintained in Dulbecco's modified Eagle's medium supplemented with 10% v/v fetal bovine serum (Gibco BRL, MD, U.S.A.). Cells were exposed to either normoxic conditions (normoxia group: 20% O_2, 5% CO_2, with N_2 balance at 37°C) or hypoxic conditions (hypoxia group: 0–0.1% O_2, 5% CO_2, with N_2 balance at 37°C) for 24 h. The hypoxic culture condition was introduced by using a CulturePal kit provided by Mitsubishi Gas Chemical Company (Tokyo, Japan). The treated H9c2 cells were washed with PBS and collected for transcriptome analysis or Western blot analysis.

Rat Heart Failure Model and Cell Cultures. Transcriptome Analyses Plasma RNA was isolated using the mirVana PARIS kit (Ambion, TX, U.S.A.) as described previously.[14,19] As an internal reference, a known amount of a synthetic artificial miRNA was included in plasma samples as described previously.[12,14] Total RNA was extracted from H9c2 and mononuclear cells or tissues with TRIzol reagent (Invitrogen, CA, U.S.A.) as described previously.[28]

The expression profiling of 375 miRNAs was performed using the ABI TaqMan Rodent MicroRNA Array kit (Card A: Applied Biosystems, CA, U.S.A.) according to the manufacturer's instructions. U6 small nuclear RNA included in the TaqMan Rodent MicroRNA Array was used as an endogenous control. No cut-off point was used. The ABI Prism 7900 HT Sequence Detection System (Applied Biosystems) was used for amplification and detection. The C_T value was obtained from the amplification plot using SDS software (Applied Biosystems).

The expressions of miR-210 and BNP mRNA were measured using the TaqMan microRNA real-time reverse transcription-polymerase chain reaction (RT-PCR) kit[29] (Applied Biosystems) and the TaqMan gene expression assay kit (Applied Biosystems) as described previously.[14,19] The 7500 Fast Real-Time PCR System (Applied Biosystems) was used for amplification and detection. The C_T values were obtained from the amplification plot using SDS software.

ISCU Western Blot Analysis A rabbit polyclonal antibody against rat ISCU was obtained from Santa Cruz Biotechnology (CA, U.S.A.). H9c2 cells or tissues of Dahl salt-sensitive rats were homogenized in Triton-based lysis buffer, and the protein concentration was determined using the bicinchoninic acid method (Pierce, IL, U.S.A.). Equal amounts of protein (5 μg) were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (12%) and transferred to a nylon membrane (GE Healthcare, Buckinghamshire, U.K.). After blocking with 5% bovine serum albumin (BSA), the membranes were incubated with the primary antibody (1 : 1000 dilution) overnight at 4°C. Membrane-bound antibodies were visualized using horseradish peroxidase-conjugated secondary antibodies (1 : 10000 dilution for 1 h). The expression levels were quantified by densitometry (Luminescent Image Analyzer LAS-1000: FUJIFILM, Tokyo, Japan).

Plasma BNP ELISA Plasma BNP concentrations were assayed using the AssayMax Rat BNP-45 ELISA Kit (AssayPro, MO, U.S.A.) according to the manufacturer's protocol. Absorbance at 450 nm was measured using a Wallac 1420 ARVO MX/Light system (PerkinElmer, MA, U.S.A.). Standard points and samples were determined in duplicate.

Assessment in Heart Failure Patients. Assessment of miR-210 Levels in Mononuclear Cells Mononuclear cells were isolated from 13 patients hospitalized for congestive heart failure (8 and 5 patients classified as New York Heart Association (NYHA) II, and NYHA III and IV, respectively, according to the NYHA functional classification system) and 6 healthy control subjects. Plasma miR-210 concentrations were not determined because these samples were derived from samples of a previous study.[19] Mononuclear cells were isolated by Ficoll-Paque Plus (Pharmacia, NJ, U.S.A.) density gradient centrifugation. The collected cells were washed 3 times with PBS. The total RNAs of mononuclear cells were extracted with TRIzol reagent and analyzed using real-time RT-PCR.

Assessment of Plasma miR-210 Levels Thirty-nine patients with heart failure were recruited from our outpatient clinic. Blood samples were collected in tubes containing EDTA as an anticoagulant, plasma was obtained, and total RNA was purified as described above. Plasma BNP

Table 1. Physiological Data of Dahl Salt-Sensitive Rats Fed the Low- and High-Salt Diets (n=9 and n=13, Respectively)

	Body weight (g)		SBP (mmHg)		Relative heart ratio (%)	Relative BNP mRNA expression
	0 weeks	8 weeks	0 weeks	8 weeks		
Low-salt diet	110.6±5.9	323.8±8.2	100.8±4.8	133.7±4.3	0.37±0.02	1.00±0.33
High-salt diet	99.9±6.3	244.4±26.1*	97.2±7.4	218.0±21.6*	0.67±0.10*	3.55±1.56*

The values represent the mean±S.D. *p<0.01. Body weight decreased in the high-salt diet group. In contrast, SBP, the relative heart ratio (heart weight/bodyweight), and BNP mRNA expression were significantly greater in the high-salt diet group than the low-salt diet group. These data show that the high-salt diet induced heart failure

Table 2. Upregulated miRNAs in the Plasma of Rats with Heart Failure

	C_T value control	C_T value heart failure	ΔC_T
miR-15a	27.35	23.74	3.61
miR-15b	27.07	24.94	2.13
miR-20a	22.13	18.94	3.19
miR-103	27.44	24.13	3.31
miR-130a	25.89	22.79	3.10
miR-130b	28.60	23.29	5.31
miR-195	23.96	20.34	3.62
miR-210	25.44	21.59	3.85
miR-301b	26.73	22.29	4.44
miR-451	25.11	20.58	4.53
miR-494	27.65	23.12	4.53

ΔC_T: C_T value of control, C_T value of heart failure.

concentrations were obtained from chart data. All patients were classified as having NYHA II heart failure caused by a previous myocardial infarction. In 24 out of 39 patients, plasma BNP concentration was reassessed during the subsequent hospital visit approximately 3 months later. The patients were divided into "improved" and "unimproved" subgroups on the basis of the changes (*i.e.*, decrease and increase, respectively) of their plasma BNP levels at the subsequent visit. Then, we evaluated whether plasma miR-210 levels at first visit could be used to predict the change in BNP.

Written informed consent was obtained from all participants. The present study was approved by the Ethics committee of the National Cerebral and Cardiovascular Center and performed in accordance with the Code of Ethics of the World Medical Association.

Statistical Analysis Data are presented as mean±S.D. Statistical analysis was performed by analysis of variance (ANOVA), regression analysis, and contingency table analysis using the JMP statistical analysis package (SAS Institute, Cary, NC, U.S.A.).

RESULTS

miRNA Array Analysis in Dahl Salt-Sensitive Rats with and without Heart Failure A high-salt diet for 8 weeks induced markedly high blood pressure and heart failure in Dahl salt-sensitive rats as reported previously.[14] SBP, the relative heart ratio, and BNP mRNA expression levels also increased with feeding of the high-salt diet (Table 1). These data demonstrate that the high-salt diet induced heart failure.

The plasma RNAs of the control and heart failure groups were then subjected to miRNA array analysis (Table 2). Eleven miRNAs including miR-210 increased significantly in the heart failure group.

Confirmation of Hypoxia-Induced miRNAs in H9c2 Cells Because heart failure is characterized by a deficiency in oxygen supply relative to peripheral oxygen demand, we hypothesized that miRNAs involved in hypoxia might be upregulated in heart failure. Therefore, H9c2 cells exposed to normoxic or hypoxic conditions were subjected to miRNA array analysis. The results showed that miR-210 expression levels increased markedly in cells under the hypoxic culture condition, which was validated by real-time RT-PCR (Figs. 1A,B). ISCU is an important target of miR-210 and the induction of miR-210 downregulates its expression.[24] However, ISCU levels in H9c2 cells did not differ between normoxic and hypoxic conditions (Fig. 1C).

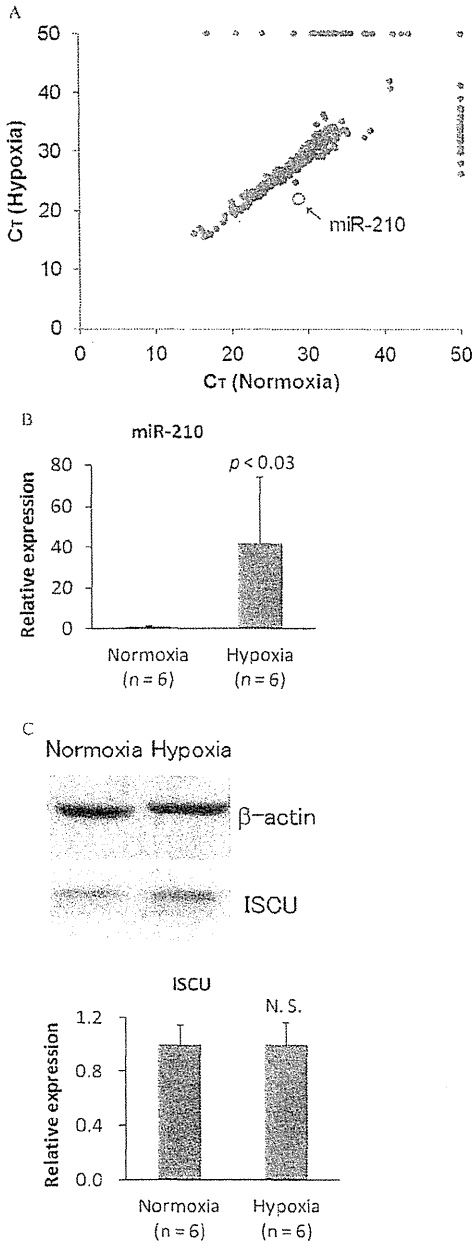

Fig. 1. Validation of miR-210 Induction in H9c2 Cells by Hypoxia

H9c2 cells were incubated under normoxic conditions (20% O_2, 5% CO_2, with N_2 balance at 37°C) or hypoxic conditions (0–0.1% O_2, 5%CO_2, with N_2 balance at 37°C). (A) MiRNAs induced by hypoxia were identified using miRNA array analysis. The correlation between the C_T values of miRNAs under normoxic and hypoxic culture conditions were assessed. MiR-210 (open circle) was highly expressed under the hypoxic culture condition. (B) The expression levels of miR-210 under hypoxic conditions were examined by real-time RT-PCR and compared with those under normoxic conditions. Hypoxia increased miR-210 levels ($p<0.03$). (C) ISCU was measured by Western blotting. Expression levels of ISCU, an important target of miR-210, were not changed. N.S., not significant. $n=6$, columns with bars represent the mean±S.D.

Assessment of miR-210 Levels in Dahl Salt-Sensitive Rats with Heart Failure Given the results of the miRNA

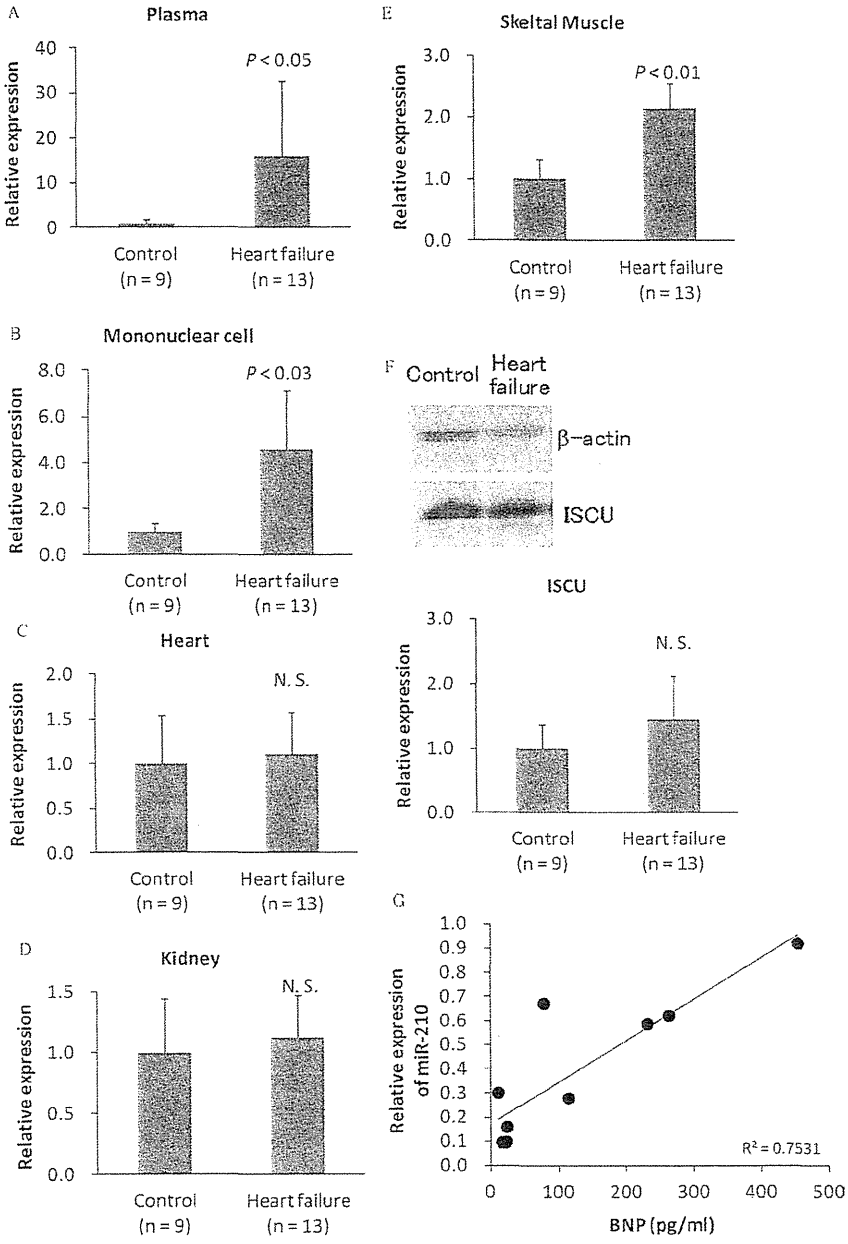

Fig. 2. Expression of miR-210, BNP and ISCU in Rats with Heart Failure

The expression levels of miR-210 in the rats fed the low- and high-salt diets were examined by real-time RT-PCR (n=9 and n=13, respectively). The columns with bars represent the mean±S.D. Control: control group, Heart failure: heart failure group. N.S., not significant. The expression levels of miR-210 were quantified in (A) plasma, (B) mononuclear cells, (C) the heart, (D) the kidneys, and (E) skeletal muscle. The expression levels of miR-210 increased 15.0 fold in plasma (p<0.05) The expression levels of miR-210 did not change in the heart and kidneys. In contrast, the expression levels of miR-210 increased 4.5 and 2.1 fold in mononuclear cells (p<0.03) and skeletal muscle (p<0.01), respectively. (F) ISCU was measured in skeletal muscle by Western blotting. ISCU levels did not change in the heart failure group. (G) Plasma BNP concentrations of rats with heart failure (n=5, 228.1±147.8 pg/mL) were significantly higher than those of without heart failure (n=5, 18.8±5.3 pg/mL, p<0.03). Moreover plasma miR-210 levels were strongly correlated with plasma BNP concentration.

array analysis in rats with heart failure and confirmation of miR-210 upregulation in cells cultured under hypoxic conditions, we investigated whether miR-210 is a biomarker for heart failure. Thus, we examined miR-210 expression levels in rats fed the low- (Control: n=9) and high-salt diets (Heart failure: n=13). Expression levels of miR-210 increased up to 15.0 fold in plasma (Fig. 2A). The miR-210 expression levels of mononuclear cells, the heart, the kidneys, and skeletal muscle were examined in order to clarify the tissues in which miR-210 levels increased. Although miR-210 expression levels were unchanged in the heart and kidneys (Figs. 2C, D), they increased up to 4.5 and 2.1 fold in mononuclear cells and skeletal muscle, respectively (Figs. 2B, E). However, ISCU expression was not downregulated in Dahl salt-sensitive rats with heart failure (Fig. 2F).

Then, rats with and without heart failure were prepared

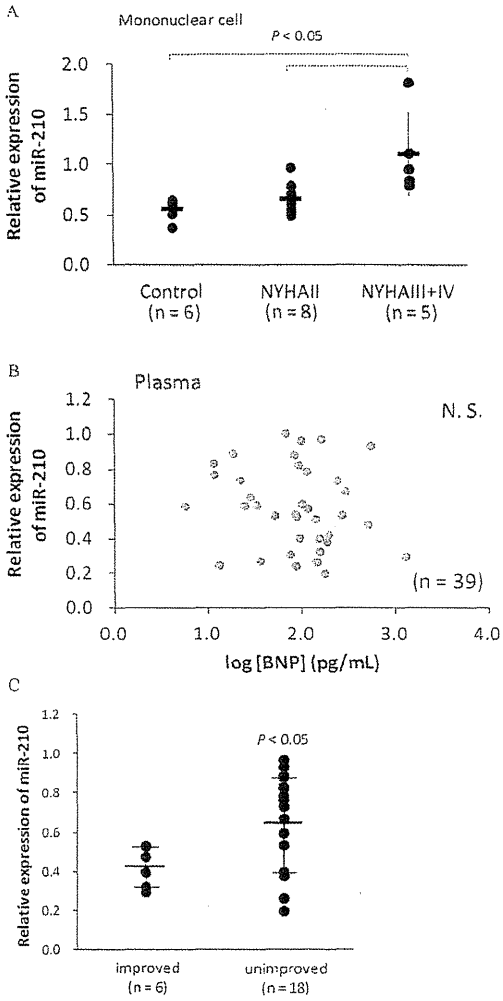

Fig. 3. Assessment of Plasma miR-210 Levels in Patients with NYHA II Heart Failure

(A) Expression levels of miR-210 in patients with severe heart failure. Expression levels of miR-210 in mononuclear cells were significantly higher in patients with NYHA III and IV heart failure than in those with NYHA II or healthy controls. Control group: n=6, NYHA II heart failure group: n=8, NYHA III and IV heart failure group: n=5. p<0.05. (B) Correlation between miR-210 and BNP levels in human plasma. Linear regression analysis. BNP levels were obtained from chart data. All patients were classified as having NYHA II heart failure caused by a previous myocardial infarction. The plasma expression levels of miR-210 were plotted against plasma BNP levels. Plasma miR-210 levels were not correlated with plasma BNP levels. N.S., not significant. (C) Classification of improved patients according to plasma miR-210 levels. The patients were divided into improved and unimproved subgroups on the basis of BNP fluctuation. Patients with a reduction in plasma BNP concentration at the subsequent visit were classified as "improved." Six patients were improved; their plasma miR-210 levels were lower (0.42±0.10, n=6). On the other hand, plasma miR-210 levels in the unimproved group were 0.65±0.25 (p<0.05).

(n=5 and n=5, respectively) in order to assess the correlation between plasma BNP and miR-210 levels. The plasma BNP concentrations of rats with heart failure (228.1±147.8 pg/mL) were significantly higher than those without heart failure (18.8±5.3 pg/mL, p<0.03). Moreover, plasma miR-210 levels were strongly correlated (r^2=0.7531) with plasma BNP, a conventional marker of heart failure (Fig. 2G).

Assessment of Plasma miR-210 Levels in Patients with Heart Failure We hypothesized that miR-210 is upregulated in patients with severe heart failure. Indeed, the miR-210 expression levels in mononuclear cells were significantly higher in patients with NYHA III and IV heart failure than those with NYHA II or healthy controls (Fig. 3A, p<0.05). However, the miR-210 expression levels in mononuclear cells were not significantly different between healthy controls and patients with NYHA II heart failure.

Table 3. Characteristics of Patients with NYHA II Heart Failure

	Patients
Sex (male/female)	39 (33/6)
Age (years)	70.7±12.3
BNP (pg/mL)	161.4±242.5
Creatinine (mg/dL)	1.12±0.74
BMI	23.1±6.1

The values represent the mean±S.D

Accordingly, 39 patients with NYHA II heart failure were recruited from our outpatient clinic. Their characteristics are summarized in Table 3. The correlation between plasma BNP and miR-210 levels was examined: no significant correlation was observed in these patients (Fig. 3B). However, plasma BNP concentrations were reassessed at the subsequent hospital visit approximately 3 months later; consequently, plasma miR-210 levels of all the improved patients were in the lower range (0.42±0.10, n=6) than those of not improved patients (0.65±0.25, n=18, p<0.05). As a result, no patients with higher plasma miR-210 level had a tendency to improve (Fig. 3C).

DISCUSSION

Based on the result of increased miR-210 by hypoxia in the *in vitro* experiment, we showed that plasma miR-210 may be available to know the condition of heart failure. Additionally, we found that the information obtained from the measurement of plasma miR-210 levels is different from plasma BNP concentration.

miRNA array analysis of the plasma of Dahl salt-sensitive rats with heart failure revealed various candidate biomarker miRNAs, including miR-15a, miR-15b, miR-20a, miR-103, miR-130a, miR-130b, miR-195, miR-210, miR-301b, miR-451, and miR-494 (Table 2). The miR-15 family (*i.e.*, miR-15a, miR-15b, and miR-195) has been reported to regulate the postnatal mitotic arrest of cardiomyocytes.[30] Meanwhile, the miR-130 family (*i.e.*, miR-130a and miR-130b) has been reported to enhance HIF-1α translation,[31] while miR-494 has been reported to activate the Akt pathway, which confers protective effects against ischemia/reperfusion-induced cardiac injury.[32] MiR-20a has been reported to modulate the translation of E2F transcription factors that regulate cell proliferation and apoptosis.[33] However, the physiological functions of miR-103 and miR-301b are still incompletely understood. Therefore, these may be worth investigating in further detail in future studies.

The miRNA array data of the rats were compared with those of the human sample obtained from a previous study.[19] The results show that rats and humans with severe heart failure exhibited upregulated plasma miR-210 and miR-451 levels. MiR-451 is highly expressed in erythroid cells[34]; hemolysis, which is frequently observed in congestive heart failure, appears to be the reason for the upregulation of plasma miR-451 in heart failure. Therefore, we focused on miR-210 as a possible biomarker for congestive heart failure.

miR-210 is well known to be upregulated by hypoxia.[35,36] It is also reported that miR-210 is regulated *via* both HIF-dependent[37,38] and HIF-independent mechanisms,[39] and that miR-210 is associated with angiogenesis.[40] Indeed, the present results confirm the induction of miR-210 by hypoxia. Chronic heart failure is characterized by a deficiency in oxygen supply relative to the demand of the peripheral tissues. Thus, from this perspective, miR-210 might be the promising candidate biomarker for heart failure.

The plasma miR-210 levels were increased in Dahl salt-sensitive rats with heart failure induced by 8 weeks of high-salt diet feeding. miR-210 expression levels of mononuclear cells, the heart, the kidneys, and skeletal muscle were examined in order to elucidate the tissues in which miR-210 was elevated. The expression levels of miR-210 did not change in the heart or kidneys. This is probably because the heart and kidneys were not exposed to hypoxic conditions, because the blood flow to these organs might be preferentially preserved.

In contrast, miR-210 expression levels in mononuclear cells and skeletal muscles increased significantly. The skeletal muscles may be the first target of reduced blood supply in congestive heart failure.[41] The increased plasma miR-210 levels might be attributable to increased miR-210 levels in the skeletal muscle.

Moreover, we assessed the correlation between plasma BNP and miR-210 levels. The results show that plasma miR-210 levels were strongly correlated with plasma BNP, a conventional marker of heart failure. Therefore, the results suggest that plasma miR-210 levels are a prognostic biomarker for chronic heart failure.

Next, we assessed miR-210 expression in human patients with heart failure. The expression levels of miR-210 in the mononuclear cells of patients with NYHA III and IV heart failure were significantly higher than those with NYHA II heart failure and healthy controls. However, miR-210 expression levels in mononuclear cells did not differ between healthy controls and patients with NYHA II heart failure. Furthermore, no significant correlation was observed between BNP and miR-210 plasma levels in patients with NYHA II heart failure. Thus, it is conceivable that the results of the present animal experiment are close to those observed in severe heart failure (NYHA III and IV) patients before medical treatment. Furthermore, the results suggest that the lower correlation in human samples could be attributed to medical treatments. However, none of the patients with higher plasma miR-210 levels showed a tendency toward improved BNP levels. Therefore, plasma miR-210 level is an auxiliary prognostic biomarker for chronic heart failure.

In the aging population, deaths and medical costs attributable to heart failure are increasing rapidly. Managing patients with heart failure is one of the greatest challenges our aging society faces. Therefore, the development of accurate prognostic biomarkers of heart failure is important. Plasma BNP level is an excellent biomarker for assessing patients with heart failure. Plasma BNP levels mainly reflect the degree of ventricular overload,[42] and are, therefore, an excellent prognostic biomarker for heart failure.[43] Because miR-210 is significantly induced by hypoxia, miR-210 levels may reflect a mismatch between the pump function of the heart and oxygen demand in the peripheral tissues. In this sense, plasma miR-210 is a potential prognostic biomarker for heart failure in addition to plasma BNP level. However, since the number of samples in the present study was insufficient to determine a suitable plasma miR-210 cut-off point and the assessment of severe patients was not carried out, a larger clinical study is required to confirm this hypothesis. In addition, although mononuclear cells might be suitable for diagnosis, this would be impractical because isolating these cells is inconvenient.

The biological significance of miR-210 induction by hypoxia remains unclear. It has been reported that ISCU is one of the direct targets of miR-210 and is downregulated by hypoxia-induced miR-210 in cancer cell lines.[38] However, miR-210 induction did not suppress ISCU protein levels under hypoxic conditions in our experiments using rat myocardial cells. Moreover, miR-210–knockout mice are reported to exhibit no gross phenotype.[44] Therefore, further studies are required to fully clarify the biological functions of miR-210.

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Lecture

解　説

心臓移植患者の運動療法*

築瀬正伸**　後藤葉一***

Key Words：heart transplantation, cardiac rehabilitation

はじめに

心臓移植患者に対する運動療法効果に関する報告は1980年代からみられ，運動時最大心拍数，運動量，最大酸素摂取量の増加や安静時心拍数の減少が報告されている．1999年には心臓移植患者を無作為に運動療法群と対照群に分けた研究が報告された．この報告では，心臓移植後早期に開始される運動療法は自然回復を超えて有意に運動能力を改善することが明らかにされている．したがって，心臓移植後患者に対して運動療法・心臓リハビリテーション(心リハ)を実施することはきわめて重要である．

心臓移植後患者は，血流遮断による移植心機能の低下，拒絶反応，免疫抑制剤による易感染性，免疫抑制剤の副作用，除神経心による生理学的特性などの問題を有するので，これらを考慮した運動処方および生活指導が必要となる．また，心臓移植術前は長期にわたる待機期間を経るため(表1)，術前の運動療法および退院後の社会的・心理的サポートも重要である．心臓移植患者に対する運動療法は，移植心の生理学を理解した上で実施する必要がある．移植心は求心性神経切断により，レニン-アンジオテンシン-アルドステロン(RAA)調節系が弱まり，心室充満圧の変化に対する正常の血管調節反応が妨げられる．また，副交感神経支配がなくなることにより安静時心拍数は増加し，交感神経支配がなくなるために運動開始時の心拍数や収縮能の応答も低下する．また，移植心は前負荷依存ともいえ，Frank-Starling機序により移植心機能は制御されていることも重要である．国立循環器病研究センター(NCVC)では，心リハのプログラムは手術後の時期により急性期，回復期，維持期の3つに分けられ，その目的や内容が異なるため，移植部と心臓血管内科，病棟と心リハ室の部門間の連携による継続的・包括的な心リハを実践している．NCVCでの心リハを紹介し，今後増加する心臓移植患者への心リハの役割を展望する．

表1　NCVCにおける心臓移植(2012.9.30現在)

症例数	50
移植時年齢	14～61(平均37)歳
性別	男性：39，女性：11
原病	拡張型心筋症：32 拡張相肥大型心筋症：8 虚血性心筋疾患：2 その他：8
待機状況	Status 1：50〔LVAS：45(90%)〕
LVAS	体外設置型；Nipro-Toyobo：39 植込み型；HeartMate VE：2, Novacor：1, EVAHEART：1, Jarvik-2000：1, HeartMate II：1
待機期間	29～3,838(平均：1,049)日 〔Status 1：29～1,476(平均：812)日〕
LVAS補助期間	39～1,703(平均：886)日

LVAS：左心補助人工心臓

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心臓移植後患者の特徴

心臓移植後患者に対する運動療法は，「心血管疾患におけるリハビリテーションに関するガイドライン(2007年改訂版)」においてクラスIIa(エビデンスレベルB)とされており[1]，術前の長期にわたるデコンディショニング(身体脱調節)のために運動療法が必須である．しかしながら，安全かつ有効に運動療法を行うために，移植心に特有な循環系反応などに配慮した運動の指導が必要となる．心臓移植手術は，病的心臓を切除し，提供されたドナーの心臓を同所性に吻合する方法が通常本邦では用いられている．心臓が非自己の心臓に換わるために，種々の因子が心機能に影響する．移植心は心臓を摘出するという手術の操作によって「除神経」されるため，心臓に対する自律神経支配がなくなり，運動に対する心臓の応答が通常と異なることがあげられる．さらに移植心とレシピエントのサイズマッチの問題，拒絶反応による心機能低下，ステロイドを含む免疫抑制剤による影響(血圧上昇など)，長期の心不全や臥床による高度のデコンディショニング，高度の身体的・精神的ストレスを経験することによる将来に対する強い不安など多くの特徴を有しており，これらを考慮した運動処方が必要となる．

移植心の心機能について

心臓移植を受けたレシピエントの運動耐容能は，良い場合でも同性・同年代の一般健常者の60～70%程度といわれている．その理由として可能性があげられているのは，レシピエントの年齢，性，BMI，変時作用の低下，拡張機能障害，アドレナリン様シグナルの欠如，細胞内カルシウムハンドリングの変化，移植後血管障害，内皮機能不全，および骨格筋異常などが指摘されている[2]．

心機能を前負荷に大きく依存する移植心においては，心機能を制御する重要な要素としてFrank-Starling機序があげられる．移植心の運動開始初期における反応は，まず骨格筋のポンプ作用と呼吸の増大，および末梢血管抵抗の低下により静脈還流が増大することにより前負荷が増大し，

表2　心臓移植における正常と異なる循環系の反応

1. 安静時心拍数の増加
2. 運動開始時における心拍数増加の遅れ
3. 運動終了後における安静時心拍数への回復の遅れ
4. 安静時左室駆出率低下
5. 運動時右室および左室駆出率低下
6. 運動時心拍出量低下
7. 運動時の動静脈血酸素較差増加
8. 最大酸素摂取量の低下
9. 最大運動能力の低下
10. 低強度運動時の酸素摂取動態
11. 嫌気性代謝閾値の低下
12. 酸素および二酸化炭素の運動時呼吸代謝率増加
13. 運動時の左室拡張末期圧上昇
14. 運動時肺動脈圧・肺動脈楔入圧・右房圧の上昇
15. 運動時左室収縮末期および拡張末期容積の増加

(文献[1]より引用)

その結果，Frank-Starling機序により一回拍出量が増加する．この機序による一回拍出量の増加は20%までであるが，さらに運動を継続した場合には，循環血中カテコラミンの増加による変時性および変力性反応によって心拍出量が増加する．このため，運動時に心拍数が増加して定常状態に達するまで通常心では2～3分であるが，除神経心では6～10分を要する．この運動に対する遅延した反応は移植後時間を経過するに従い改善することが報告されている．本邦では，右心房を温存するBicaval法(わが国ではmodified Bicaval法)が用いられることが多く，従来の右心房で吻合するLower-Shumway法と異なり，ドナー心の右房機能が維持される．

運動時における移植心の反応は，表2に示すように正常心とは異なっているが[3]，通常の日常生活を送る場合は特に問題がないことが知られており[4]，心臓移植後にフルマラソンを完走した症例も報告されている[5]．

除神経心について

除神経心は運動に対して特異的な反応を示す．求心性神経切断により，心室充満圧の変化に対する正常の血管調節反応が妨げられることにより，心血管系の恒常性が変化する．さらに，心筋虚血時の胸痛症状もみられなくなることに注意が必要となる．副交感神経支配がなくなることにより安静時の心拍数は増加する．反面，交

表3 NCVCにおける心臓移植後心リハの効果(CPX成績の変化)

	移植前	1か月後	3か月後
Peak load(W)	70±16.6	78.6±22.9	91.2±24.7*
Peak HR(bpm)	110±26.1	120±14.0	125±15.5
Peak $\dot{V}O_2$(ml/kg/min)	13.6±3.6	17.4±5.1	21.3±4.7*
Peak $\dot{V}O_2$ % predict	33.4±9.1	43.4±13.3	53.2±12.2*
AT(ml/kg/min)	8.6±1.4	9.3±1.8	11.3±2.0*
$\dot{V}E/\dot{V}CO_2$ slope	34.8±6.5	35.5±7.4	32.0±4.3

*：1か月後対3か月後 $P<0.05$(第18回日本心臓リハビリテーション学会シンポジウムより)

感神経支配がなくなるために，運動開始時の心拍数や収縮能の急激な変化もみられなくなる．運動時における心機能の増強は，もっぱら循環血中カテコラミンの増加による心筋のβアドレナリン作用受容体の刺激によってもたらされる[3][6][7]．

心臓移植後の運動療法

1．心臓移植後の運動療法の効果について

心臓移植後の運動療法の効果について記述された論文をいくつか紹介する．

36例の男性心臓移植患者(平均47歳)において，移植後平均7か月後から16か月間，歩行・走行による運動療法を行った．その結果，平均8.5分/kmのペースで24km/週の運動が行えるようになり，体重が2.4kg，運動時最大心拍数が12.7bpm，運動量が49%，最大酸素摂取量(peak oxygen uptake：peak $\dot{V}O_2$)が27%増加した．また，安静時の心拍数は平均3.6bpm減少した[8]．

同意の得られた27例の心臓移植患者を無作為に運動療法群と対照群に分け，運動療法群には退院後から有酸素運動療法を6か月間継続した．その結果，両群とも運動能力は改善したが，peak $\dot{V}O_2$，最大負荷量の増加は対照群に比べて運動療法群でいずれも有意に大であった．さらに，安静時心拍数の減少，嫌気性代謝閾値までの時間，一定時間に行える起立負荷回数の増加にも有意差がみられたことから，心臓移植後早期に開始される運動療法は自然回復を超えて有意に運動能力を改善した[9]．

20例の女性心臓移植患者に12週間の有酸素運動とレジスタンストレーニングを実施した結果，運動療法開始前の体力は，年齢による予測値と比較して50%ほど低かったが，12週後は6分間歩行ならびに下肢筋力が有意に増加し，男性と同様の運動療法効果をもたらした[10]．

NCVCにおいても，心臓移植後に心リハを導入した11例において，心肺運動負荷試験検査(CPX)の成績が向上したことを報告している(表3)．

以上のように，心臓移植術後の運動療法によって，心臓移植後患者の運動耐容能や下肢筋力の向上が期待され，NCVCでは，心臓移植後の患者に対しても積極的に運動療法を導入している．しかし，特異的な注意点もいくつか存在する．

2．心臓移植後の運動療法において注意すべき点

(1)心臓移植後急性期における運動療法

心臓移植後急性期における運動療法の注意点として，以下のことがあげられる．

①免疫抑制療法および易感染性(拒絶反応と感染)
②除神経によるドナー心機能の特性
③虚血によるドナー心機能への影響
④長く低心拍出症候群(LOS)状態にあったことによる諸臓器機能の低下および低栄養状態

この時期に特に注意を要するのが「感染」である．術後3か月以内に最も多く，症状が潜行することがあり，感染の予防が特に重要となる．NCVCにおける心臓移植後のクリーン度(抜粋)を表4に示すが，感染予防の観点からクリーン度が高い時期(クリーン度I～III度，術後3週間程度)は，クリーンルーム内または移植病棟内までと行動範囲が狭く，また多くの症例で補助人工心臓装着部の創部の状態が安定していないことなどに注意を要する．それでも表5に示すように，術後可能な限り早期から，長期安静臥床による合併症(褥創，関節拘縮，筋萎縮など)を防止し，精神的ストレスを軽減することを目的と

表4　NCVCにおける心臓移植後のクリーン度

クリーン度	I度	II度	III度	IV度	V度	VI度
	・移植後1週間(原則) ・重症急性拒絶反応 ・重症感染症	・移植後1回目の心筋生検あるいは移植後1週まで ・強い免疫抑制療法中 ・易感染状態(白血球減少など)	・移植後1回目の心筋生検で治療を要する拒絶反応がなく，移植後1週間経過 ・免疫抑制療法が安定(プレドニン30mg/日以下)	・移植後3週目相当の心筋生検で治療を要する拒絶反応がない(プレドニン20mg/日以下)	・移植後5週目相当の心筋生検で治療を要する拒絶反応がない(プレドニン15mg/日以下)	・リハビリなどで移植後長期治療が必要であり，術後3か月を経過 ・移植後検査入院時
外出	不可		クリーン内の廊下	病棟内～病院内(検査時のみ)	病院内	

表5　心臓移植後の急性期リハビリテーションプログラム

＜第1段階＞循環動態安定後
　安静度：自動体交，受動座位90度可
　運　動：自動運動(筋力低下が著しいときは他動的屈伸運動を行う)
＜第2段階＞端座位・立位負荷試験後
　安静度：ベッド上
　運　動：端座位となり足踏み練習1日3回5分間
＜第3段階＞室内歩行(2分間)負荷試験後
　安静度：病室内
　運　動：病室内歩行練習1日3回10分間
＜第4段階＞エルゴメーター20W 5分間負荷試験後
　運　動：エルゴメーター20W 5分間1日2回
＜第5段階＞100m歩行負荷試験後
　安静度：病室内，クリーンルーム内ロビー歩行可
　運　動：100m歩行練習1日3回
＜第6段階＞200m歩行負荷試験後
　安静度：病棟内
　運　動：200m歩行練習1日3回
＜第7段階＞500m歩行負荷試験後
　安静度：病院内自由
　運　動：500m歩行練習1日3回
＜第8段階＞心血管疾患リハビリテーション
　運　動：心臓リハビリテーション室にて行う

(文献1)より抜粋，一部改変)

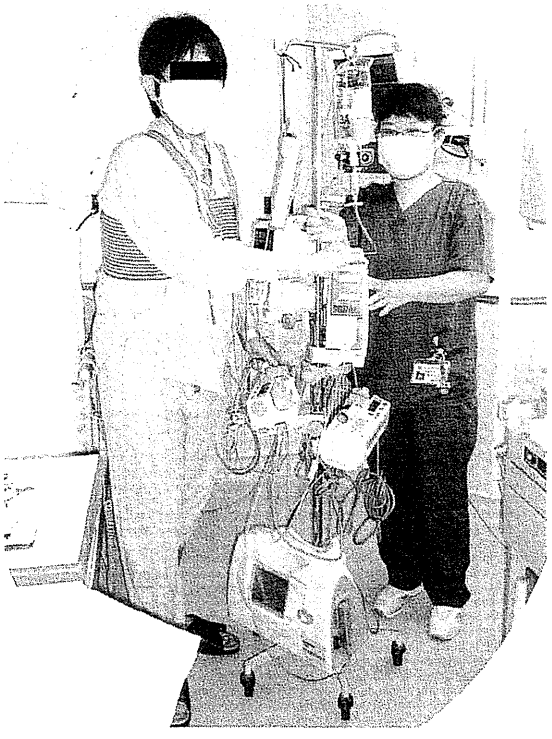

図1　病室(クリーンルーム)内リハビリテーション風景
点滴や体外式ペーシング，VAC療法中の病室内リハビリテーション．

して，早期離床，移植病棟内歩行やエルゴメータを用いた運動を行う(図1,2)．心臓移植後3週間目の心筋生検で拒絶反応を認めず，クリーン度がIV度になり(表4)，500メートル歩行負荷終了後は心臓リハビリテーション病棟で運動療法に参加させる．

(2)心臓移植後の回復期における運動療法

回復期は，急性期に引き続きさらに可動範囲を拡大して運動能力を高めるとともに，不安・抑うつ・自信喪失などの精神的障害を改善し，より良い身体的・精神的状態で社会復帰することを目的として行う．運動療法のプログラムは，NCVCでは，基本的には通常の心臓術後患者および心不全患者のリハビリテーションプログラムに準じて施行している(図3)．心臓に対する自律神経支配がないため心拍数を指標にした運動

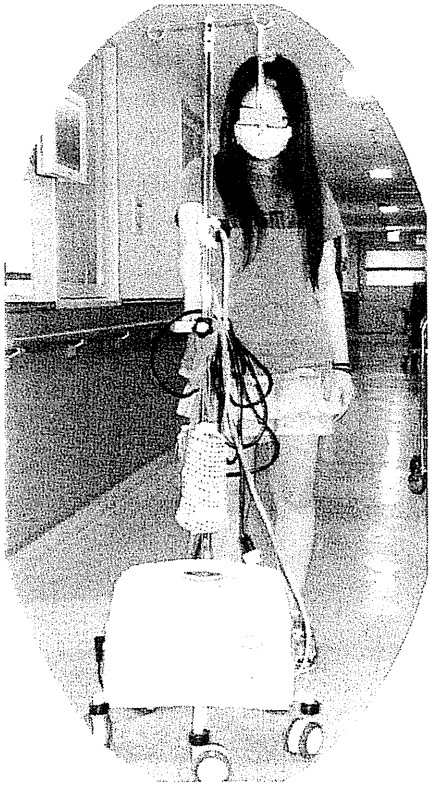

図2　病棟(移植病棟)内リハビリテーション風景
VAC療法中の病棟内リハビリテーション.

図3　心臓リハビリテーション室でのリハビリテーション風景
心血管疾患における監視型心臓リハビリテーション.

強度の設定が困難であり，自覚的運動強度および酸素摂取量($\dot{V}O_2$)に基づいて運動強度の設定を行うようにしており，CPXの結果により運動強度を設定する場合には，peak $\dot{V}O_2$の40～60％程度を目安として行っている．退院時には心リハ担当医より退院後の運動療法について説明し，在宅運動療法の指導を行っている．退院後は在宅運動療法に加え，可能な限り外来通院型心リハプログラムに参加するよう指導している．回復期の心リハ終了時には再度CPXを施行し，運動耐容能の改善度を評価するとともに，この結果から維持期の在宅運動処方を更新している．

(3)心臓移植後維持期における運動療法

維持期の運動療法の目的は，回復期運動療法により得られた良好な身体的・精神的機能を，社会復帰後生涯にわたって維持し，快適で質の高い生活を送ることを目的としている．具体的には非監視下に在宅運動療法を継続する．運動処方は回復期プログラム終了時に行ったCPXの結果に基づいて，心リハ担当医により決定され，説明される．

ま と め

心臓移植後の患者は，長期の待機期間中に起こる筋肉量の低下やデコンディショニングのため，移植後早期は運動能力が低下したままであることが多い．したがって，積極的な運動療法・心臓リハビリテーション(心リハ)が有効であり，これによってより円滑で質の高い社会復帰が可能となる．国立循環器病研究センターでは心臓移植後，77％の患者が社会復帰を果たし，21％が回復期・維持期の運動療法を実施している(2012年9月30日現在)．今後心臓移植の増加に伴い，心臓移植後患者の心リハの重要性はますます高まっていくものと思われる．

文　献

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Ⅲ.2 次予防と薬物療法（心イベント後の薬物療法）

心臓リハビリテーションと薬物療法
～両者の兼ね合いをどうする～

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慢性心不全に対する標準的治療法として，β遮断薬・アンジオテンシン変換酵素（angiotensin converting enzyme；ACE）阻害薬・アンジオテンシンⅡ受容体拮抗薬（angiotensin Ⅱ receptor blocker；ARB）などによる薬物療法がほぼ確立されている．近年，これに加えてデバイス治療・運動療法（心臓リハビリテーション）・和温療法などの非薬物療法のエビデンスが蓄積され，ガイドラインにおいて推奨されるようになった結果，現在では薬物療法と非薬物療法の併用の機会が増加している．ところが，薬物療法と非薬物療法との併用に関して記述した書物は意外に乏しく，現場で対応に苦慮することも少なくない．本章では，慢性心不全に対する運動療法と薬物療法の併用に関して，基本的概念・臨床的効果・注意点について述べる．

なお，本章で頻出する「運動療法」と「心臓リハビリテーション」の区別について，「運動療法」とは運動処方に基づく運動トレーニングプログラムを指す一方，「心臓リハビリテーション」とは運動療法に加えて食事療法・生活指導などの患者教育・カウンセリング・心不全管理を含む包括的プログラムを指すものであり，類似するものであるが同一ではないことに留意されたい．

慢性心不全治療に運動療法が必要な理由

慢性心不全における運動耐容能低下

American College of Cardiology（ACC）/American Heart Association（AHA）[1] および日本循環器学会[2] の慢性心不全ガイドラインに述べられているとおり，慢性心不全とは単なる左室収縮機能の低下ではなく，労作時呼吸困難・息切れなどの症状により生活の質（quality of life；QOL）低下や日常生活制限が生じた臨床症候群である．したがって，慢性心不全の治療においては，生存率や左室収縮機能の改善だけではなく，労作時呼吸困難などの症状の軽減と運動耐容能・QOL の改善も重要な治療目標とするべきである．

ところが，これまでの研究により，慢性心不全患者の運動耐容能［最高酸素摂取量（peak VO_2）］は左室駆出率（left ventricular ejection fraction；LVEF）とは相関せず，むしろ骨格筋量や筋力と相関することが知られている[3]．さらに，心不全の標準治療薬であるβ遮断薬やACE 阻害薬・ARB の運動耐容能改善効果は乏しい[4-6]．これは，慢性心不全患者の運動耐容能低下の直接的な原因が安静時の LVEF 低下ではなく，過剰な安静による身体デコンディショニング，低灌流による骨格筋エネルギー代謝異常，炎症性サイトカイン上昇による筋萎縮［心臓悪液質（cardiac cachexia）］，内皮依存性血流増加反応低下，自律神経機能低下などの末梢機序[3] に由来す