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Sex Hormone and Gender Difference—Role of Testosterone on Male Predominance in Brugada Syndrome

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Testosterone in Brugada Syndrome. ***Introduction:*** **The clinical phenotype is 8 to 10 times more prevalent in males than in females in patients with Brugada syndrome. Brugada syndrome has been reported to be thinner than asymptomatic normal controls. We tested the hypothesis that higher testosterone level associated with lower visceral fat may relate to Brugada phenotype and male predominance.**

Methods and Results: **We measured body-mass index (BMI), body fat percentage (BF%), and several hormonal levels, including testosterone, in 48 Brugada males and compared with those in 96 age-matched control males. Brugada males had significantly higher testosterone (631 ± 176 vs 537 ± 158 ng/dL; P = 0.002), serum sodium, potassium, and chloride levels than those in control males by univariate analysis, and even after adjusting for age, exercise, stress, smoking, and medication of hypertension, diabetes, and hyperlipidemia, whereas there were no significant differences in other sex and thyroid hormonal levels. Brugada males had significantly lower BMI (22.1 ± 2.9 vs 24.6 ± 2.6 kg/m^2; P < 0.001) and BF% (19.6 ± 4.9 vs 23.1 ± 4.7%; P < 0.001) than control males. Testosterone level was inversely correlated with BMI and BF% in both groups, even after adjusting for the confounding variables. Conditional logistic regression models analysis showed significant positive and inverse association between Brugada syndrome and hypertestosteronemia (OR:3.11, 95%CI:1.22–7.93, P = 0.017) and BMI (OR:0.72, 95%CI:0.61–0.85, P < 0.001), respectively.**

Conclusions: **Higher testosterone level associated with lower visceral fat may have a significant role in the Brugada phenotype and male predominance in Brugada syndrome.** *(J Cardiovasc Electrophysiol, Vol. 18, pp. 415-421, April 2007)*

Brugada syndrome, gender, sex hormones, testosterone, body mass index

Introduction

Brugada syndrome is characterized by coved-type ST-segment elevation in the right precordial electrocardiographic (ECG) leads (V1–V3) and an episode of ventricular fibrillation (VF) in the absence of structural heart disease.[1-5] The prevalence of the disease is estimated to be up to 5 per 10,000 inhabitants and is one of the important causes of sudden cardiac death of middle-aged males, particularly in Asian countries including Japan.[4]

More than eight dozen distinct mutations in *SCN5A*, the gene encoding the α subunit of the sodium channel, have been so far identified in patients with Brugada syndrome and all mutations display an autosomal-dominant mode of transmission.[6,7] Therefore, males and females are expected to inherit the defective gene equally. However, more than 80% of patients in Western countries and more than 90% of patients in Asian countries affected with Brugada syndrome are males.[8] Recent experimental studies have unveiled the cellular mechanism of Brugada phenotype. The male predominance in the Brugada syndrome is suggested to be due, at least in part, to intrinsic differences in ventricular action potential (AP) between males and females.[9]

A male hormone, testosterone is reported to increase net outward currents[10-12] and is expected to accentuate Brugada phenotype, such as ST-segment elevation and subsequent episodes of VF in patients with Brugada syndrome. Testosterone is also known to decrease visceral fat.[13-15] Since patients with Brugada syndrome have been reported to be

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thinner than asymptomatic normal controls by Matsuo et al.,[16] we speculated that higher testosterone level associated with lower visceral fat may modulate Brugada phenotype and may relate to male predominance in patients with Brugada syndrome.

Methods

Patient Population and Data Collection

The study population consisted of 48 males with Brugada syndrome who agreed to participate in this study and showed Type 1 "coved" ST-segment elevation in V1–V3 leads[17] ranging in age from 30 to 69 years with a mean age of 50 ± 11 years (mean ± SD). Brugada males who were less than 30 years old and more than 70 years old were excluded from this study to minimize the influence of age on the basal sex hormonal levels including testosterone. Forty of the forty-eight Brugada males have been included in our previous clinical studies.[18-20] In all patients, physical examination, chest roentgenogram, laboratory values, echocardiography with wall motion analysis, and Doppler screening excluded structural heart diseases. The clinical, electrocardiographic, and electrophysiologic characteristics of the 48 Brugada males are shown in Table 1. Average age of the 48 Brugada males at diagnosis was 47 ± 12 years old. Aborted cardiac arrest or VF was documented in 21 males (44%), syncope alone in 11 males (23%), and 16 males (33%) were asymptomatic. Family history of sudden cardiac death (SCD) was observed in eight males (17%). An *SCN5A* coding region mutation was identified in seven (17%) of 42 males in whom genetic screening was conducted. Implantable cardioverter defibrillator (ICD) was implanted in all 32 symptomatic males with documented VF and/or syncope. ICD was also implanted in nine of 16 asymptomatic males due to induction of VF during the electrophysiologic study. Type 1 ST-segment elevation was recorded spontaneously in 43 males (90%) and was induced by sodium channel blockers in five males (10%). Complete right bundle branch block was observed in three males (6%). Late potential was recorded by a signal-average ECG system in 27 (59%) of 46 males. During the electrophysiologic study, VF requiring direct cardioversion for termination was induced in 32 (73%) of 44 males. Average HV interval was 46 ± 11 msec.

TABLE 1
Clinical, Electrocardiographic, and Electrophysiologic Characteristics in the 48 Brugada Males

Clinical characteristics	
Age at diagnosis (years)	47 ± 12
Aborted cardiac arrest or VF (%)	21/48 (44%)
Syncope alone (%)	11/48 (23%)
Asymptomatic (%)	16/48 (33%)
Family history of SCD	8/48 (17%)
SCN5A mutation	7/42 (17%)
ICD implantation	41/48 (85%)
Follow-up period (month)	41 ± 2
Arrhythmic event (%)	9/48 (19%)
Electrocardiographic characteristics	
Spontaneous coved-type ST elevation	43/48 (90%)
CRBBB (%)	3/48 (6%)
RR (msec)	939 ± 113
PQ interval (II) (msec)	186 ± 34
QRS duration (V2) (msec)	104 ± 18
Corrected QT interval (V5) (msec)	394 ± 27
ST amplitude at J point (V2) (mV)	0.32 ± 0.16
Late potential (%)	27/46 (59%)
Electrophysiologic characteristics	
Induction of VF	32/44 (73%)
Mode (Triple/Double/Single)	16/15/1
HV interval (msec)	46 ± 11

CRBBB = complete right bundle branch block; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; VF = ventricular fibrillation.

We first obtained data, such as the hormonal levels, visceral fat parameters, and ECG parameters in the 48 Brugada males prospectively between January and July in 2003, mainly at regular outpatient clinics for checking ICD. Only a Brugada male refused to participate during the recruitment of the case.

Thereafter, age-matched control males were randomly selected from the municipal population registry in Suita City. The hormonal and visceral fat data were collected sequentially between August and December in 2003. The municipal population registry in Suita City included 5,846 control subjects, among whom 1,052 males were age-matched to the 48 Brugada males. The 96 control males with a mean age of 50 ± 11 years were sequentially recruited from the age-matched 1,052 males. None of the recruited 96 control males refused to participate in this study. There were no significant differences in the clinical characteristics between the 96 control males and the remaining 956 age-matched males. Therefore, we had no way of knowing the body weight of the individuals who were selected to serve as controls from a very large database. Although K. Matsuo is a co-author of this study, none of the Brugada males and control males who appeared in the article by Matsuo[16] are included in the present study population.

All protocols were approved by the Ethical Review Committee in the National Cardiovascular Center. Written informed consent was obtained from all subjects.

Sex and Thyroid Hormonal Levels and Serum Electrolytes

Blood samples for analysis of basal hormone levels and serum electrolytes were obtained between 8:00 and 9:00 AM after an overnight fast. Plasma sex hormonal levels including testosterone, estradiol, DHEA-S, LH, and FSH were measured using commercially prepared immunoassay kits (testosterone, LH, and FSH: Chemiluminescent immunoassay [Bayer HealthCare, New York, NY, USA]; estradiol: Electrochemiluminescent immunoassay [Roche Diagnostics GmbH, Mannheim, Germany]; DHEA-S: Radioimmunoassay [Diagnostic Products Corporation, Los Angeles, CA, USA]). Thyroid hormonal levels including free T3, T4, and TSH, and serum electrolyte levels including sodium, potassium, and chloride were also measured.

Body Mass Index and Body Fat Percentage

Body weight (BW) was measured to the nearest 0.1 kg and height to the nearest cm. Body-mass index (BMI) was calculated as weight/height^2 (kg/m^2) as a parameter of visceral fat. We also measured body-fat percentage (BF%) by using body composition analyzer (Biospace Co., Ltd. Tokyo, Japan). These visceral fat parameters were measured just after blood sampling. In the 32 symptomatic Brugada males who had had documented VF and/or syncope, the BW and BMI were also measured within 48 hours after their clinical events during admission in our hospital or other emergent hospitals.

ECG Parameters

In the 48 males with Brugada syndrome, 12-lead ECG was recorded just before blood sampling, and ECG parameters were assessed by an investigator (WS) blinded to clinical information. The ECG parameters included RR interval, PQ interval measured in lead II, QRS interval measured in lead V2, QT interval, corrected QT (QTc) interval measured in leads V5, and ST amplitude at J point measured in lead V2.

Statistical Analysis

We first conducted univariate analysis by using unpaired *t*-test to compare each data between the Brugada males and the control males. Since several confounding variables, such as age, exercise (none, sometimes, regularly), stress (none, sometimes, regularly), current smoking (no, yes), and medication (no, yes) of hypertension, diabetes, and hyperlipidemia may affect the hormonal levels including testosterone level and the visceral fat parameters, analysis of covariance (ANCOVA) was used to compare least square mean values between the Brugada males and the control males adjusting for these confounding variables. Pearson's correlation coefficients were calculated between the testosterone level and the visceral fat parameters. Partial correlation coefficients were calculated between the testosterone level and the visceral fat parameters after adjusting for age, exercise, stress, current smoking, and medication. Moreover, conditional logistic regression models were used to calculate odds ratios and 95% confidence intervals adjusting for age, BMI, exercise, stress, current smoking, hypertension, diabetes, and hyperlipidemia. Hypertestosteronemia was defined as serum testosterone levels $\geq$700 ng/dL, which is 75 percentiles of testosterone levels among case and control combined groups. In the 32 Brugada males with documented VF and/or syncope, a paired *t*-test was used to compare the visceral fat parameters at the clinical cardiac events and at the measurement of hormonal and visceral fat data. A two-sided P value below 0.05 was considered to indicate significance. All statistical analyses were performed by using SAS software, Ver 8.2.

Results

Hormonal Levels, Serum Electrolytes, and Visceral Fat

Table 2 illustrates univariate analysis for comparing sex and thyroid hormonal levels, serum electrolytes, and visceral fat parameters between the two groups. Testosterone level was significantly higher in the Brugada males than in the control males, whereas there were no significant differences in other sex hormonal levels; estradiol, DHEA-S, LH, FSH, and thyroid hormonal levels; T3, T4, and TSH. Serum sodium, potassium, and chloride levels were all significantly higher in the Brugada males than in the control males. BMI, BF%, and BW were all significantly lower in the Brugada males than in the control males. All variables followed normal distribution, both in the 48 Brugada and 96 control males.

The comparison of the confounding variables that may affect the hormonal levels and the visceral fat parameters between the 48 Brugada males and the 96 control males was shown in Table 3. Even after adjusting for age, exercise, stress, current smoking, and medication (hypertension, diabetes, and hyperlipidemia), the testosterone level, serum sodium, potassium, and chloride levels were all significantly higher, and the visceral fat parameters were significantly lower in the 48 Brugada males than in the 96 control males (Table 4). There were also significant differences in these parameters between the 24 definite Brugada males with documented VF and/or *SCN5A* mutations and the 96 control males after adjusting for the confounding variables (Table 4).

Correlation between Testosterone, Visceral Fat, and Serum Electrolytes

Testosterone level was inversely correlated with all visceral fat parameters, BMI, BF%, or BW in both the Brugada males and the control males, even after adjusting for age,

TABLE 2

Sex and Thyroid Hormonal Levels, Serum Electrolytes, and Visceral Fat Parameters in the 48 Brugada Males and the 96 Age-Matched Control Males

	Brugada Males (n = 48)	Control Males (n = 96)	P Value
Sex hormones			
Testosterone (ng/dL)	631 ± 176	537 ± 158	0.002
Estradiol (pg/mL)	28.9 ± 7.6	31.1 ± 12.6	0.263
DHEA-S (ng/mL)	1,901 ± 850	1,966 ± 861	0.668
LH (mIU/mL)	4.6 ± 2.6	3.9 ± 2.0	0.073
FSH (mIU/mL)	6.2 ± 4.9	5.0 ± 2.9	0.066
Thyroid hormones			
Free T3 (pg/mL)	3.3 ± 0.4	3.4 ± 0.3	0.360
Free T4 (ng/dL)	1.3 ± 0.1	1.3 ± 0.2	0.089
TSH (μIU/mL)	1.9 ± 1.4	1.7 ± 1.4	0.619
Serum electrolytes			
Sodium (mEq/L)	143.7 ± 2.0	142.6 ± 2.0	0.003
Potassium (mEq/L)	4.6 ± 0.3	4.3 ± 0.3	<0.001
Chloride (mEq/L)	105.1 ± 2.1	103.6 ± 2.1	<0.001
Viceral fat			
BMI (kg/m^2)	22.1 ± 2.9	24.6 ± 2.6	<0.001
BF% (%)	19.6 ± 4.9	23.1 ± 4.7	<0.001
BW (kg)	62.9 ± 9.7	70.0 ± 8.6	<0.001

Values are mean ± SD where indicated.
BMI = body-mass index; BF% = body-fat percentage; BW = body weight.

TABLE 3

Comparison of the Confounding Variables Between the 48 Brugada Males and the 96 Age-Matched Control Males

	Brugada Males (n = 48)	Control Males (n = 96)	P Value
Exercise			
None (%)	39.6	44.8	
Sometimes (%)	41.6	43.8	
Regularly (%)	18.8	11.5	0.482
Stress			
None (%)	27.1	21.9	
Sometimes (%)	54.2	54.2	
Regularly (%)	18.8	24.0	0.684
Current smoking (%)	25.0	27.1	0.789
Medication			
Hypertension (%)	20.8	19.8	0.883
Diabetes (%)	2.1	13.5	0.028
Hyperlipidemia (%)	10.4	5.2	0.246

TABLE 4
Testosterone, Serum Electrolytes, and Visceral Fat Parameters in the Brugada Males and the 96 Age-Matched Control Males after Adjusting for Confounding Variables

	Brugada Males	Control Males (n = 96)	P Value
ALL Case (n = 48)			
Testosterone (ng/dL)	631 ± 44	538 ± 40	0.003
Sodium (mEq/L)	144.2 ± 0.5	143.2 ± 0.5	0.007
Potassium (mEq/L)	4.6 ± 0.1	4.3 ± 0.1	<0.001
Chloride (mEq/L)	105.5 ± 0.5	103.9 ± 0.5	<0.001
BMI (kg/m^2)	22.3 ± 0.7	24.9 ± 0.7	<0.001
BF% (%)	20.0 ± 1.3	23.9 ± 1.1	<0.001
BW (kg)	63.4 ± 2.4	70.1 ± 2.1	0.001
Definite Brugada case with VF and/or *SCN5A* (n = 24)			
Testosterone (ng/dL)	656 ± 59	550 ± 48	0.009
Sodium (mEq/L)	143.9 ± 0.7	142.9 ± 0.6	0.042
Potassium (mEq/L)	4.7 ± 0.1	4.4 ± 0.1	<0.001
Chloride (mEq/L)	105.2 ± 0.7	103.9 ± 0.6	0.006
BMI (kg/m^2)	21.5 ± 1.0	24.5 ± 0.8	<0.001
BF% (%)	19.9 ± 1.7	24.1 ± 1.4	<0.001
BW (kg)	60.5 ± 3.1	69.2 ± 2.5	0.001

Values are mean ± SE adjusted for age, exercise, stress, current smoking, and medication of hypertension, diabetes and hyperlipidemia. BMI = body-mass index; BF% = body-fat percentage; BW = body weight; VF = ventricular fibrillation.

exercise, stress, current smoking, and medication (Brugada: BMI, r = –0.394, P = 0.011; BF%, r = –0.390, P = 0.012; BW, r = –0.335, P = 0.032; Control: BMI, r = –0.333, p = 0.002; BF%, r = –0.333, P = 0.001; BW, r = –0.305, P = 0.004), suggesting that Brugada males had higher testosterone level associated with lower visceral fat compared with control males (Fig. 1). No significant correlations were observed between other serum electrolytes and testosterone level or visceral fat parameters. Testosterone level was not correlated with age, even after adjusting for exercise, stress, current smoking, and medication (r = 0.007, P = 0.947).

Conditional Logistic Regression Models Analysis

Conditional logistic regression models analysis showed significant positive and inverse association between Brugada syndrome, hypertestosteronemia (Odd Ratio (OR): 3.11, 95%CI: 1.22–7.93, P = 0.017), and BMI (OR: 0.72, 95%CI: 0.61–0.85, P < 0.001), respectively (Table 5). Other variables did not significantly increase or decrease risks of Brugada syndrome (Table 5).

Visceral Fat at Clinical Cardiac Events in Brugada Males

In the 32 symptomatic Brugada males with documented VF and/or syncope, the time-span between the clinical cardiac events and the measurement of hormonal and the visceral fat data was 42 ± 32 months (mean ± SD, 1–99 months). The BMI and BW at the clinical cardiac events (VF or syncope) were significantly lower than those at the measurement of hormonal and visceral fat data (BMI, 21.0 ± 2.6 vs 22.1 ± 2.9 kg/m^2; BW, 60.0 ± 8.9 vs 62.9 ± 9.7 kg: P < 0.001, respectively).

Testosterone versus ECG Parameters, Symptoms or SCN5A Mutation in Brugada Males

Baseline electrocardiographic data of the 48 Brugada males are shown in Table 1. No significant correlations were observed between testosterone level and ECG parameters, including ST amplitude (r = –0.123, P = 0.406) and QTc interval (r = –0206, P = 0.160), in the 48 Brugada males. There was no significant difference in testosterone level between 32 symptomatic and 16 asymptomatic Brugada males (649 ± 185 vs 593 ± 157 ng/dL: P = 0.298). No significant difference was observed in testosterone level between 43 Brugada males with spontaneous Type 1 ST-segment elevation and five Brugada males with sodium channel blocker-induced Type 1 ST-segment elevation (624 ± 171 vs 688 ± 230 ng/dL: P = 0.448). Testosterone level was also no different between seven Brugada males with *SCN5A* mutation and 41 Brugada males without *SCN5A* mutation (700 ± 198 vs 619 ± 172 ng/dL: P = 0.261).

Follow-Up

Arrhythmic events occurred in nine (19%) of 48 Brugada males during average follow-up periods of 41 ± 2 months after blood sampling for the present study (Table 1). In more detail, arrhythmic events appeared in eight (38%) of 21 Brugada males with a history of aborted cardiac arrest or VF, in one (9%) of 11 Brugada males with syncope alone, but did not appear in any (0%) of 16 asymptomatic Brugada males.

Discussion

The major findings of the present study were: (1) Brugada males had significantly higher testosterone level, serum sodium, potassium, and chloride level, and significantly lower BMI, BF%, and BW than those in control males by univariate analysis, even after adjusting for age, exercise, stress, current smoking, and medications related to hypertension, diabetes and hyperlipidemia. (2) Testosterone level was inversely correlated with the BMI, BF%, and BW in both Brugada males and control males, even after adjusting for the confounding variables. (3) Conditional logistic regression models analysis showed strong positive association between Brugada syndrome and higher testosterone level (hypertestosteronemia) and strong inverse association between Brugada syndrome and BMI.

Testosterone in Brugada Phenotype and Male Predominance

For the past decade, numerous clinical, experimental, and molecular genetic studies have elucidated Brugada syndrome as a distinct clinical entity.[1-5,17] However, several problems remain unresolved, such as genetic heterogeneity, ethnic difference, and gender difference.[7] Di Diego and Antzelevitch recently suggested the cellular basis for male predominance in Brugada syndrome by using arterially perfused canine right ventricular wedge preparations.[9] Transient outward current (I_{to})-mediated phase 1 AP notch was larger in male dogs than in female dogs in the right ventricular epicardium, but not in the left ventricular epicardium, responsible for the male predominance in the Brugada phenotype. Recent clinical studies suggested that male hormone testosterone might be attributable to gender difference of the prevalence in this

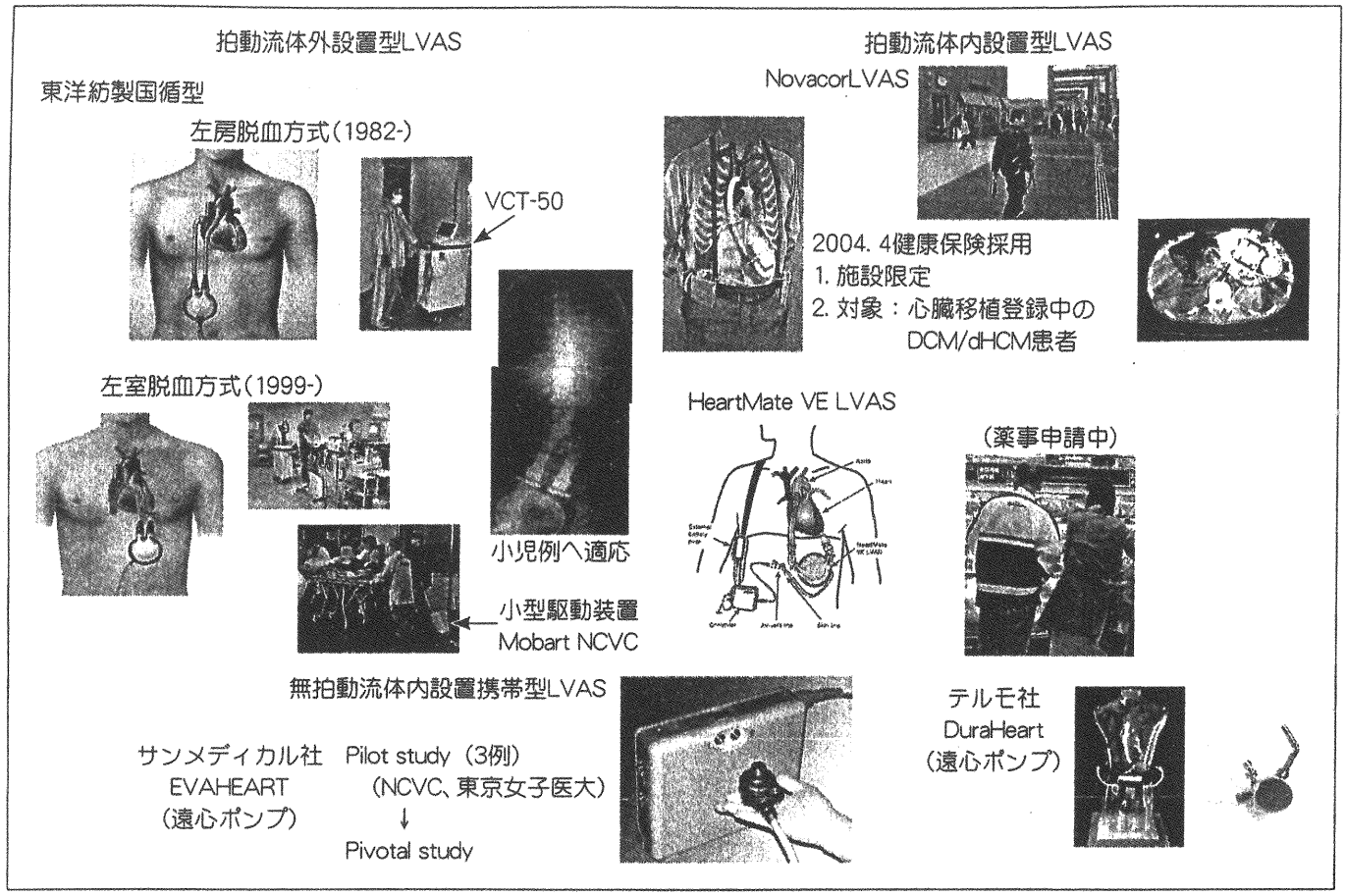

図1　臨床応用されている各種補助人工心臓

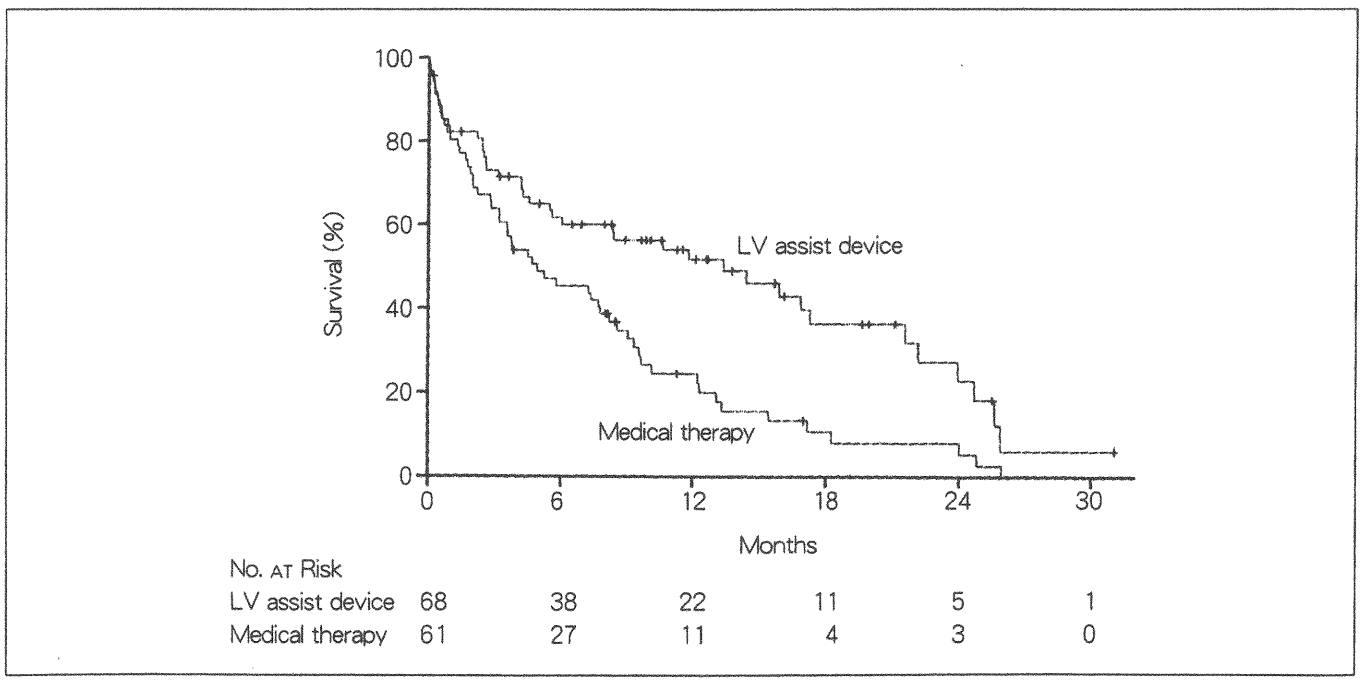

図2　REMATCH studyにおける左心補助人工心臓装着例と内科的治療における累積生存率（文献7より）

ギー源と接続する．体側に装着した小型制御装置およびバッテリーにより活動性が良好となり，在宅療法が可能である．この2種は体重70～80 kg前後の成人男性を想定して開発されており，血液ポンプのサイズが大きい．このため，対象は体表面積1.5m^{2}以上の患者で，小さな体格の人への適応は困難であ

る．なお，Novacorは，2004年4月に心臓移植へのブリッジ用として，日本臓器移植ネットワークに登録し高度先進医療として複数例の心臓移植を経験している施設に入院している拡張型心筋症および拡張相肥大型心筋症患者への適応が，健康保険で認められた．また，HeartMate-VEは治験が終了し，薬事承認申請中である．

補助循環の適応とシステムの選択

高度心不全例に対する循環補助法には，IABP，PCPSおよびVASがある[3]．IABPやPCPSは経皮的装着可能である．このためCCU等において簡便に用いられ，ある程度の補助効果が期待できる．しかし，IABPは自己心機能に依存しており補助能力に限界がある．また，PCPSは，左室の直接的な減負荷が行えず，左室機能高度低下例では肺水腫を来しやすい．また，両者とも長期施行が困難である．これに対し，VASは装着時開胸手術が必要であるが，心機能の100%代行が可能である．

このため，循環補助を適応する場合には，個々のシステムの特徴を理解して選択する必要があり，適応判定時にIABPやPCPSの補助能力を越えていると判断される症例では直接VASの適応を考慮する．表1にVAS適応基準を示すが，血行動態の指標に加え重要臓器など全身状態への配慮が重要で，不可逆性の腎・肝障害，敗血症，中枢神経疾患，高度の出血傾向がある症例は除外される[4,5]．心機能の回復が期待し難い例では，次の治療選択である心臓移植の適応についても検討が必要となる．また，VASが適応となる重症心不全例では，長期の補助を必要とすることが多く，また心臓移植待機となる可能性があるため，治療選択において本人および家族へのインフォームド・コンセントが重要となる．従ってVASの適応決定においては時間を要することを念頭において，対応する必要がある．

適応するシステム選択では，右心不全が問題となる．高度右心不全がない症例では左心補助のみで対応する．この場合，体格が大きい（体表面積1.5m^{2}以上）症例では体内植込み型を考慮する．体格が小さい場合には，体外設置型の左室脱血方式を用いる．右心不全が高度である場合はLVASに加えRVASを併用した両心補助が必要で，体外設置型を選択する．なお，右心不全に対し，一酸化窒素（NO）ガスを用いることにより管理は容易となった．また，中等度以上の三尖弁逆流を認める症例においては三尖弁形成術を併用することで，右心機能改善が期待できる．

表1　重症心不全患者に対する補助人工心臓心臓の適応基準

1）左心補助人工心臓
内科的治療および／あるいはIABPに反応しない心不全
1）血行動態　PCWP≧20 mmHg
および
収縮期血圧≦80 mmHgあるいは心係数≦2.0
2）副徴　1時間排尿≦0.5 mL/kg
SvO_2≦60%
臨床経過　急激な血行動態の変化
進行する腎機能障害＊
進行する肝機能障害＊＊

2）右心補助人工心臓
左心補助人工心臓駆動下において内科的治療およびNO（一酸化窒素）吸入に反応しない右心不全
（中等度以上の三尖弁逆流を伴う場合には三尖弁形成術を併用）
CVP＜18 mmHgでは，収縮期血圧≦80 mmHgあるいは心係数≦2.0

3）適用除外
1）回復不能な腎機能障害
2）回復不能な肝機能障害
3）呼吸不全（循環不全に伴うものは除く）
4）高度な血液障害（出血傾向など）
5）重症感染症
6）インフォームドコンセントがとれない場合
（特に慢性心不全の急性増悪例）

＊：進行する腎機能障害の指標
BUN≧40 mg/dLおよび／あるいはクレアチニン≧2mg/dL
1時間排尿≦0.5 mL/kg（利尿剤の使用下）
＊＊：進行する肝機能障害の指標
総ビリルビン≧2.0 mg/dLおよび／あるいはSGOT≧200 U/L

VAS装着例における管理

VAS装着後は，循環動態と全身状態の安定化を計る[4,6]．全身状態が安定化すれば，早期抜管を図る．

また，感染の危険性を減少させるため，経口摂取を開始し，種々のラインの早期抜去を試みる．早期からリハビリテーションを開始し，ベッド上での受動運動から筋力に応じて運動量を増し，病室内での日常生活を行えるようにする．さらに，全身状態の改善に応じて，徐々に自転車こぎや病棟内歩行などを加える．

VAS駆動法は，固有レートかfull-fill to full-emptyモードを選択する．カウンタパルゼイション法は，自己心への負荷を軽減し回復を促進するのに有効と考えられるが，VAS装着例では不整脈が頻発する場合が多く，不整脈時にポンプの駆動が休止するため，十分な補助量を得難い．また，常時安定した心電図を得ることは困難である．

全身状態改善後は，ACE阻害剤やβブロッカーを含む内科的心不全治療を再開する．適宜，心エコー法やBNP測定などにより自己心機能を評価し，自己心機能に応じ補助量減少や，運動量増大など自己心のトレーニングを計る．補助量減少や運動量増大しても自己心機能が良好である場合，VASからの離脱を考慮する．当施設での左室脱血方式LVASの離脱基準を**表2**に示す．

VAS施行中の抗血栓療法[5]は，外科的出血コントロール後に開始する．経口摂取が早期から開始できる症例ではワーファリンを用いる．目標PT-INRは術後早期では2とし，安定期には3～4前後に維持する．早期にワーファリンが開始できない症例や，PT-INRのコントロールに難渋する症例ではヘパリン（通常低分子ヘパリン）を併用する．また，術後早期から抗血小板療法を併用する．通常はアスピリン81を1錠／日投与し，血小板機能に応じて投与量を調整する．我々は血小板機能としてずり応力下血小板血栓形成能を測定している．また，脳出血時への対応が重要で，我々は乾燥人血液凝固第Ⅸ因子複合体を用いている．

VAS使用時に注意すべき合併症として，血栓塞栓症とともに感染症があり，感染予防に注意する必要がある．特に，体外設置型での送・脱血管や体内植込み型でのチューブでの皮膚貫通部や，植込まれた血液ポンプに注意する必要がある．また，長期補助例では，精神状態への配慮が必要で，精神神経科医によるサポートも含めた医療チームでの対応が重要である．

表2　LV-LVASからの離脱基準

1. 安定した全身状態
2. 正常な臓器機能（肝臓，腎臓）
3. 感染（－）
4. 低補助量で安定した血行動態
   (Pump Rate : 60 bpm)
5. 自己心機能
   心エコー：左室拡張末期径（LVDd＜55 mm）
   心拍数＜100 bpm
   Dobutamine 負荷テスト：CI＞2.5l/min/m^2
   良好な左室指標の応答性
   良好なSGカテ指標の応答性

わが国での臨床応用の現状

日本臨床補助人工心臓研究会の2005年度のレジストリーによると，これまでに780例にVASが適応されている．主な使用ポンプは東洋紡製が461例，BVS-5000が81例，植込み型（Novacor，HeartMate）が53例であった．心筋症以外の急性心不全では，補助期間は1週間（median）で，42％が離脱し，26％が生存した．心筋症への適応は1992年から開始され，267例に達している．システムは東洋紡製左室脱血型が128例で，他に東洋紡左房脱血型69例，ゼオン製16例，NovacorLVAS25例，HeartMate-IP LVAD 17例，HeartMate-VE 7例であった．平均施行日数は267（最長1245）日であった．また，東洋紡左室脱血型では平均334（最長1245）日であった．移植例は40例（国内19例，渡航21例）あり，心機能の改善を認めた36例が離脱した．

我が国で2005年末までに施行された心臓移植は29例であるが，21例がLVAS装着例であった（**表3**）．施行期間は平均666日で，最長は当施設での東洋紡製左室脱血型での1227日で，15例が1年以上の補助例であった．システムは，東洋紡製15例，Novacor LVAS 2例，HeartMate-IP 2例，-VE 2例であった．

また，当施設で心臓移植適応ありと判定した119例における1年および3年累積生存率をみると各々84％および57％であるが，死亡およびLVAS装着のイベントフリー生存率では各々52％および32％と低下し，LVASによる生存率の著明な改善を認めた．

表3　わが国における心臓移植

症例数	29例
年齢	8－61(平均37) 歳
性別	男性：22例，女性：7例
原疾患	DCM：14例，dHCM：5例，薬剤性CM：1例，心筋炎後CM：1例，ICM：1例，先天性：1例
待機状況	Status1：全例(LVAS装着：21例，強心薬持続投与：8例)
待機期間(status 1)	29－1304(平均629) 日(1年以上：22例)
LVAS補助期間	21－1227(平均666)日(1年以上：15例)
東洋紡-左房型	2例(39日，910日)
東洋紡-左室型	13例(99－1227(平均662)日(1年以上：9例))
Novacor	2例(125日，1087日)
HeartMate-IP	2例(518日，590日)
HeartMate-VE	2例(993日，1056日)
移植施設	
国立循環器病センター	15例，大阪大学：9例，東京女子医大：2例
埼玉医大：1例，九州大：1例，東北大：1例	

なお，体格の小さな症例への適応を考慮した新しいVASの開発が進められており，これまで用いられてきた拍動型に加え，流入・流出弁を必要とせず小型化が可能な無拍動流ポンプが注目され，軸流ポンプ（Jarvik 2000-flowmaker, MicroMed Debakey VAD, HeartMate II, Incorなど）の臨床治験が開始されている．また，同じく無拍動流ポンプで長期使用に有利と考えられている遠心ポンプでは，我が国で2種の体内植込み型LVASとして開発が進められており，テルモ社のシステム（図1下右）がヨーロッパで2004年より臨床応用を開始した．また，サンメディカル社のシステム（図1下左）は，我が国で臨床試験が開始され，既にpilot studyが終了し，現在pivotal studyの準備が進められている．

まとめ

補助人工心臓は，内科的および外科的治療の限界を越えた重症心不全に対し，強力な治療選択であり，心臓移植へのブリッジとともに，自己心機能の回復による離脱も期待し得る．米国で心臓移植の適応とならない末期心不全患者を対象として，体内植え込み型HeartMate-VEと最大の内科的治療の成績を比較する二重盲検試験が行われ，HeartMate－VE装着患者の成績がよかったことが報告された[7]（図2）．この結果をふまえ2003年秋には，心臓移植の適応とならない末期心不全患者に対するdestination therapyとして認められるようになっており，今後，わが国においても，心臓移植の代替手段としてのVASの適応が検討されるようになると考えられる．

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