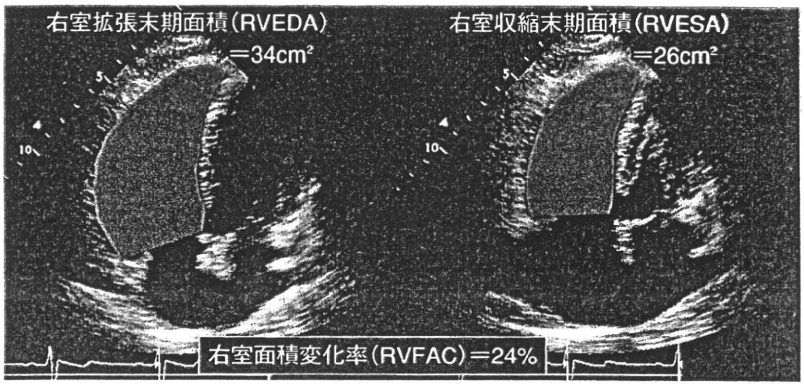
右室面積変化率(RVFAC)
RVFAC＝(RVEDA－RVESA)/RVEDA×100%で表される．ASEのガイドラインでは，RVFAC＜35％は右室収縮能低下である．この症例は，原発性肺血管性肺高血圧症の女性で，RVFAC＝24％と右室収縮能の低下を認める．
(文献4)より引用改変)



	正常範囲	軽度異常	中等度異常	重度異常
右室拡張末期面積 (cm^2)	11～28	29～32	33～37	≧38
右室収縮末期面積 (cm^2)	7.5～16	17～19	20～22	≧23
右室面積変化率 (%)	32～60	25～31	18～24	≧17

右室駆出率(3D RVEF)は52.6±9.9(32.8～62.5)％で，Cardiac MRIの計測値と良好な相関を認めたとの報告がある．ASEによる3D RVEFの正常値は(44～69％)で，3D RVEF＜44％は右室収縮能低下と考えられる．

右室機能評価に組織ドプラの僧帽弁輪運動速度波形が用いられるのと同様に，組織ドプラによる三尖弁輪運動速度波形は右心機能の評価に有用である．三尖弁輪収縮期運動速度(TVS')(図9)は右室収縮能の指標の1つとして用いられる．正常値は(15.10～19) cm/secで，TVS'＜10cm/secで右室機能障害が推測される．

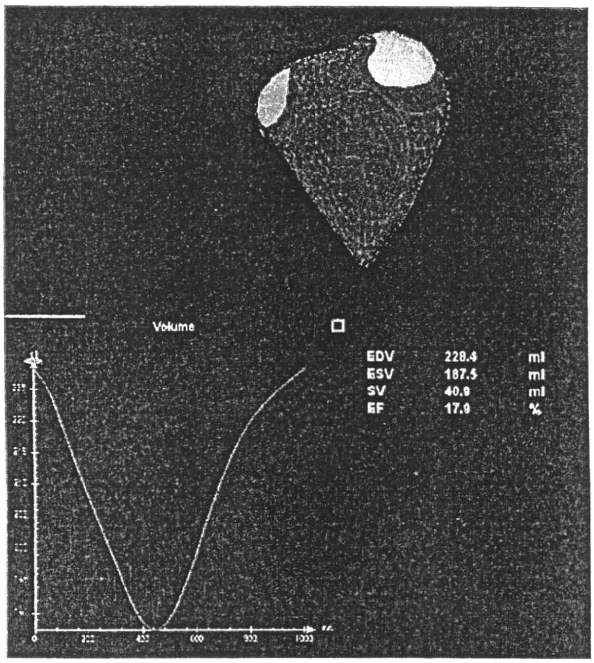


図8　3D心エコーによる右室駆出率(3D RVEF)の測定
TomTec社の3D解析ソフト(4D Real View 5.0)を用いて計測した右室容量および右室駆出率(3D RVEF)である．右室はその特異な形態のため，2D心エコーでは右室容量・駆出率の測定は困難である．それと比較して，3D心エコーによる右室駆出率(3D RVEF)は，より正確な右室容量・駆出率の測定が可能である．ASEガイドラインでは，3D RVEF≧44％が正常である．この症例は，右心不全合併の肺高血圧例で，3D RVEF＝17.9％と著明な右室収縮能低下を認めている．

(4) 右室拡張機能

肺高血圧症では，慢性の肺動脈圧上昇による右室圧負荷および容量負荷の増大により，右室拡張末期圧・右房圧が出現し，右室拡張機能障害が認められる．そして，右室拡張機能障害は，右室拡大や右室肥大が出現する前の早期の右室機能障害を鋭敏に評価できる指標であるとともに，肺高血圧症の右心不全・予後に影響する因子とされている．さらに肺高血圧症の治療効果の判定にも有用である．

右室流入血流速波形＝三尖弁血流速波形のパラメーター(TVE(三尖弁拡張早期最大血流速度)，TVA(三尖弁拡張後期最大血流速度)，TVDcT(三尖弁血流速波形の拡張早期波減速時間)，TVIVRT(三尖弁血流速波形の等容弛緩時間))，組織ドプラに

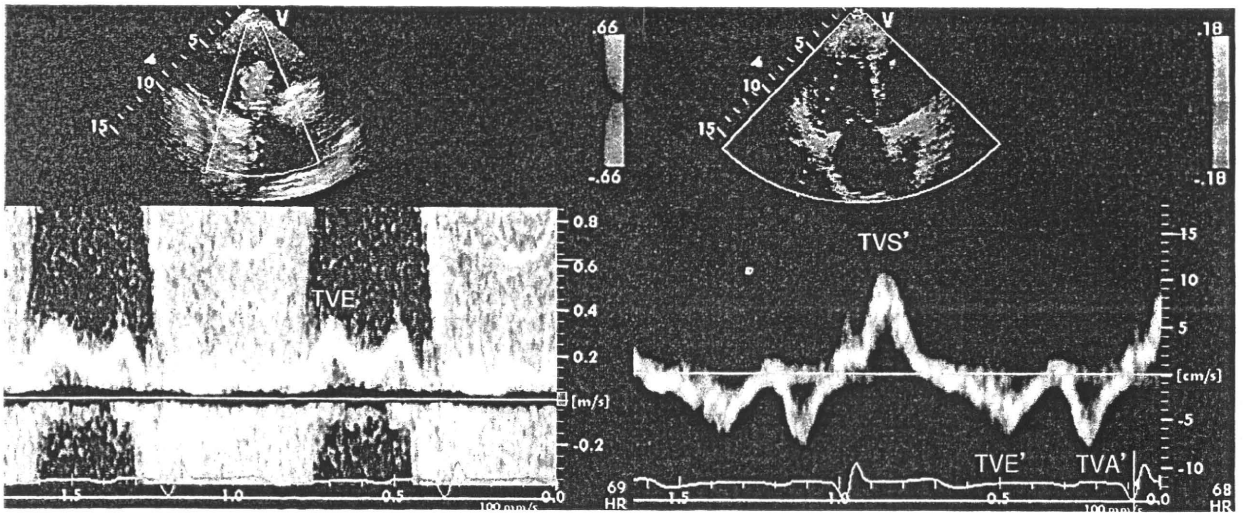


図9　三尖弁TVE/E'

左：右室流入血流速波形＝三尖弁血流速波形，右：組織ドプラによる三尖弁輪運動速波形
TVE：三尖弁拡張早期最大血流速度，TVS'：三尖弁輪収縮期運動速度，TVE'：三尖弁輪拡張早期運動速度，TVA'：三尖弁輪拡張後期運動速度

表7　右室拡張能の指標と正常値（三尖弁血流速波形と三尖弁輪運動速波形の指標）

	正常値	(95% CI)
TVE (cm/sec)	54	(35 ～ 73)
TVA (cm/sec)	40	(21 ～ 58)
TVE/A ratio	1.4	(0.8 ～ 2.1)
TVDcT (msec)	174	(120 ～ 299)
TVIVRT (msec)	48	(23 ～ 73)
TVE'(cm/sec)	14	(8 ～ 20)
TVA'(cm/sec)	13	(7 ～ 20)
TVE'/A' ratio	1.2	(0.5 ～ 1.9)
TVE/E' ratio	4	(2 ～ 6)

TVE：三尖弁拡張早期最大血流速度，TVA：三尖弁拡張後期最大血流速度，TVDcT：三尖弁血流速波形の拡張早期波減速時間，TVIVRT：三尖弁血流速波形の等容弛緩時間，TVE'：三尖弁輪拡張早期速度，TVA'：三尖弁輪拡張後期速度　（文献3）より引用改変）

よる三尖弁輪運動速度波形のパラメーター（TVE', TVA'），および右房容量が右室拡張能の指標として用いられる（図9，表7）．これらの指標は心尖部四腔断層像より求められる．右室流入血流速波形は呼気止めで，5心拍連続記録する．しかし，右室流入血流波，三尖弁輪運動速波形のパラメーターは，年齢・心拍数・呼吸により変動するので，そのことを考慮して評価する必要がある．

TVE/A＜0.8では右室弛緩障害，TVE/Aが0.8～2.1でE/E'＞6の場合がpseudonormal filling pattern，TVE/A＞2.1でTVDcT＜120msecではrestrictive filling patternと考えられる．

最近では，組織ドプラを用いたTVE/E'，右房容量，拡張期strain rateが右室拡張能評価の指標として有用とされているが，TVE/E'は2～6が正常範囲で，TVE/E'＞6が異常であり，TVE/E'＞8で右房圧≧10mmHgであるという報告もある．

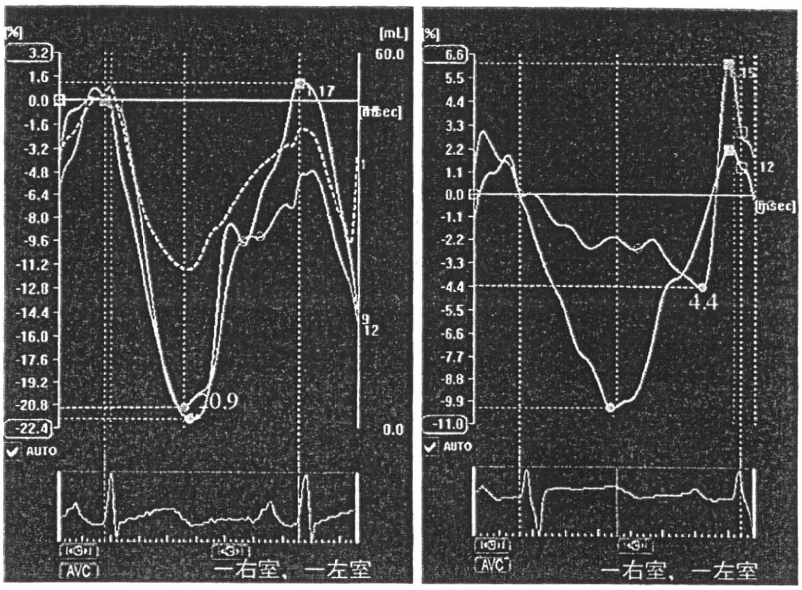
（5）右室局所心筋機能

右室心筋局所機能を評価する指標としてstrainおよびstrain rateが用いられる．組織ドプラ法および2D speckle tracking imaging法があるが，近年，角度依存性がない2D speckle tracking imaging法が使用されるようになっている．2D speckle tracking imaging法によるstrainとstrain rateは，心筋内の微小な斑点の移動距離と移動速度を自動計測し求められ，右室局所心筋機能を詳細に定量的に評価できる方法である．右室心筋の評価には，主に心尖部断層像を用いたlongitudinal strainが用いられている．肺高血圧による右室心筋の2D speckle tracking imaging法のlongitudinal strainによる解析では，右室自由壁心筋のpeak strain値の減少と，peak strainに達する時間（time to peak strain）が左室や心室中隔心筋より遅延する右室-左室の同期不全（dyssynchro-

図10　2D speckle tracking法による右室局所心筋障害の評価

左：正常例　右：原発性肺高血圧症

2D speckle tracking法を用いたlongitudinal strainによる右室および左室のmid free wallのpeak strainとpeak strainまでの時間(time to peak strain)を示す．正常例では右室と左室のtime to peak strainはほぼ一致しているが，肺高血圧症例では右室のpeak strainまでの時間は左室より遅延し，右室のdyssynchronyを示す．さらに右室のpeak strain値の低下を認める．



正常例　　原発性肺高血圧症

strain値の減少が認められる．そして，このpeak strain値の減少とtime to peak strainの遅延は，肺高血圧症が重症になるとともにさらに増悪する．われわれの肺高血圧症の2D speckle tracking imaging法によるlongitudinal strainの検討では，まず，軽症の肺高血圧例では，右室自由壁のtime to peak strainの遅延が出現する．その後，肺高血圧・右心不全が悪化するとtime to peak strainの遅延の増悪とともにpeak strain値の減少が生じる所見が得られた(図10)．またpeak strain値を微分して求めたstrain rateでも，収縮期peak strain rate値の減少が認められた．2D speckle tracking imaging法のlongitudinal strainおよびstrain rateは，肺高血圧症の右室機能を詳細に定量的に評価できる方法である．

右室自由壁中部心筋の2D speckle tracking imaging法のlongitudinal strainのpeak strain値の正常値は(mean 20～38)%であり，右室機能障害では20%以下となる．また，peak strain rate値は1.54(0.85～2.23) s^{-1}が正常で，0.85 s^{-1}未満で右室心筋収縮障害が推測される(表8)．

(6) 右室総合的心機能 (図11)

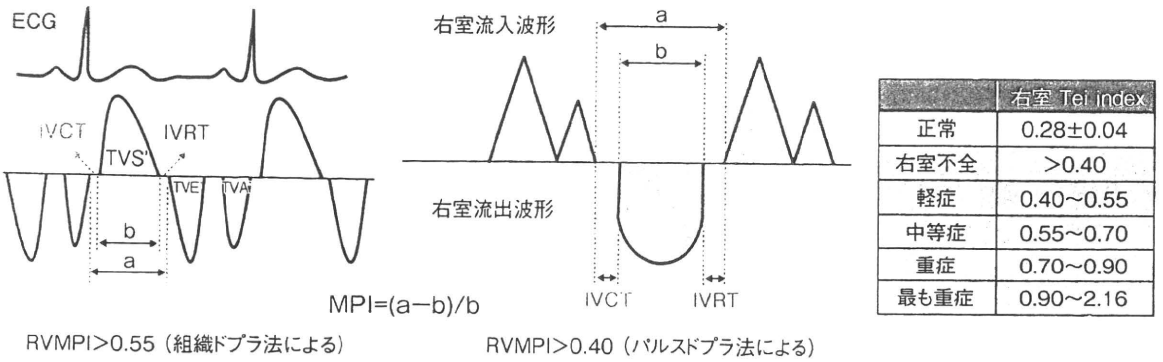
RVMPIは組織ドプラ法の三尖弁輪運動速度波形より求める方法と，パルスドプラ法による右室流入血流波形および右室流出波形より求める方法がある．パルスドプラ法によるRVMPIは右室Tei indexと同様である[7]．RVMPI＝(IVCT＋IVRT)/ETより求められ，右室の収縮および拡張能の総合的心機能の指標である．組織ドプラ法より求めるRVMPI＞0.55およびパルスドプラ法のRVMPI(右室Tei index)＞0.40は，右室機能障害の指標となる．これらの値は肺高血圧，急性肺血栓塞栓の症例で，肺動脈圧の上昇とともに増加し，感度よく右心機能障害を診断するのに有用である．ただし，これらの値は，心拍数により変動することと，右房圧が高値の場合にIVRTが短縮するため低値に出て過小評価することに注意しなければならない．

(7) 心嚢液貯留 (図12)

肺高血圧症の予後規定因子の心エコー所見として，心嚢液貯留がある[8]．肺高血圧症で右心不全が出現し慢性的に右房圧，静脈圧が上昇すると，心嚢液貯留の所見が認められる．右心機能障害が進行し右心不全が重症になるに従い，心嚢液も増量する．しかし，膠原病合併の肺高血圧症では，右心不全がなくても心嚢液貯留が認められる場合があり，必ず他の指標で右心機能評価を行うことは必要である．

表8　右室自由壁のlongitudinal strainおよびstrain rate

2D peak strain rate			2D peak strain		
variable studies	異常	正常値 (95% CI)	variable studies	異常	正常値 (95% CI)
at the base (s^{-1})	< 0.70	1.62 (0.70 ~ 2.54)	at the base (%)	< 18	28 (18 ~ 39)
at the mid cavity (s^{-1})	< 0.85	1.54 (0.85 ~ 2.23)	at the mid cavity (%)	< 20	29 (20 ~ 38)
at the apex (s^{-1})	< 0.86	1.62 (0.86 ~ 2.39)	at the apex (%)	< 19	29 (19 ~ 39)



	右室 Tei index
正常	0.28±0.04
右室不全	>0.40
軽症	0.40~0.55
中等症	0.55~0.70
重症	0.70~0.90
最も重症	0.90~2.16

図11　右室心筋パフォーマンス指標(RVMPI)(右室Tei index)
右室の収縮能，拡張能を統合した総合的右心機能指標である．
IVCT：等容収縮時間，IVRT：等容弛緩時間，ECG：心電図，S'：収縮期波，E'：拡張早期波，A'：心房収縮期波
(文献7)より引用改変)

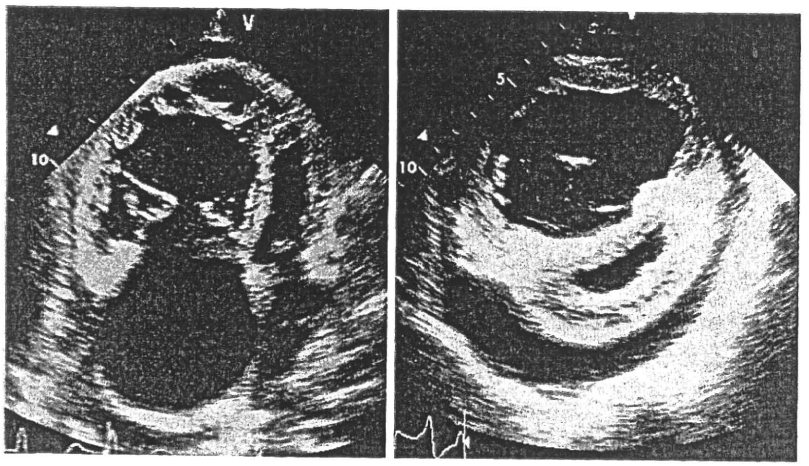


図12　重症肺高血圧症の心嚢液貯留
右心不全合併の重症肺高血圧症例．著明な右室右房拡大と右室壁肥厚とともに左室左房は狭小化し，全周性に心嚢液貯留を認める．

●三尖弁異常

肺高血圧症では，右室負荷の増大とともに右室拡大，右室機能障害が出現し，機能性三尖弁逆流が生じる．この肺高血圧症による三尖弁逆流は，左室機能障害で出現する機能性僧帽弁逆流と同様に，弁尖・弁輪自体に器質的異常はなく，右室拡大や右室機能低下による，三尖弁弁尖の乳頭筋による牽引tetheringと弁輪拡大によるものと考えられる．このような三尖弁異常の検討には，3D心エコーによる評価が有用である．今までの経胸壁3D心エコーの三尖弁について解析した研究では，正常例と比較して肺高血圧例では，三尖弁輪面積が有意に拡大し(11.3±2.3 vs 8.7±1.8cm^2)，tenting volumeも有意に増大(4.2±2.4 vs 1.1±0.6cm^2)すると報告されている[9]．当院でもワイディ社製の3D心エコー解析ソフト：REAL VIEWを用いて経胸壁3D心エコーにより記録した三尖弁の解析を行った（図

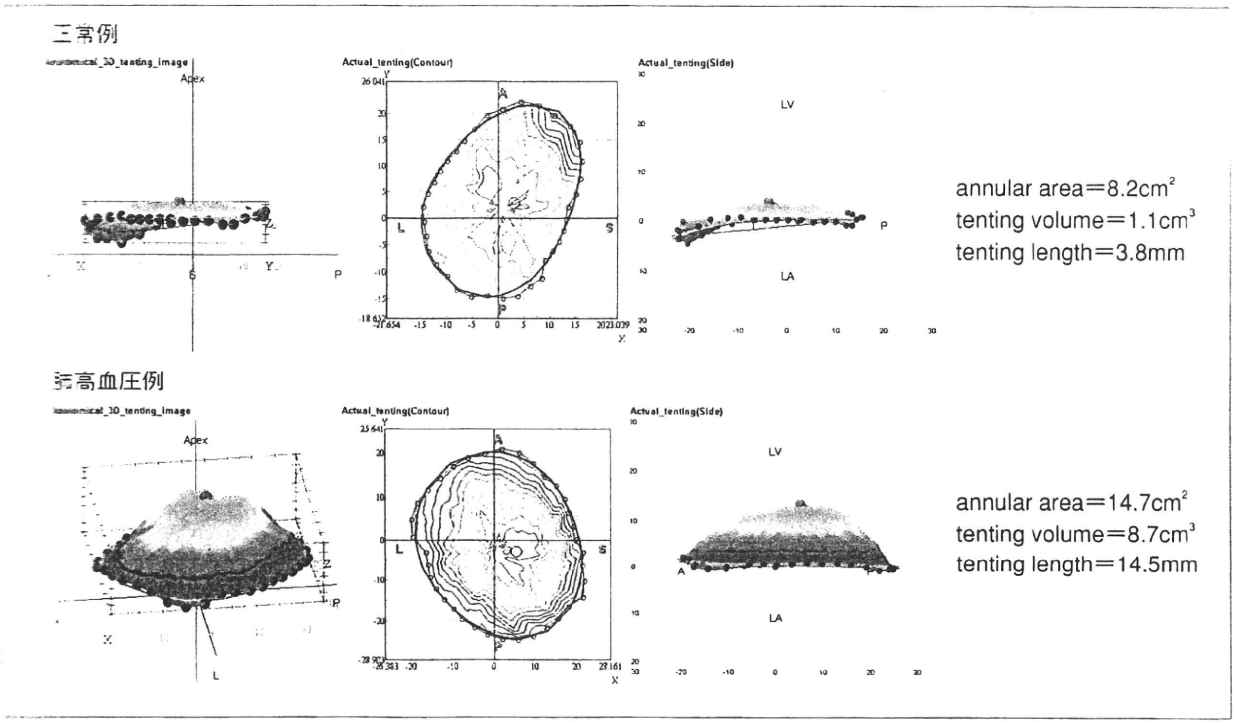


図13　3D三尖弁解析ソフト(ワイディ社製REAL VIEW)を用いた肺高血圧症による三尖弁弁輪面積の拡大およびtetheringの評価

重症三尖弁逆流を認める肺高血圧例では，三尖弁輪面積および心尖部方向へ牽引されるtenting volume, tenting lengthの増大が認められる

13）．その結果，肺高血圧症では三尖弁輪面積は増大し，tenting volume, tenting lengthも有意に増大していた．さらに，この所見は肺高血圧症の右心不全の増悪するとともに増大傾向を認めた．また，重症肺高血圧症で右室・右房の拡大と高度の三尖弁逆流を認める症例のなかに，三尖弁の一部が収縮期に右房側へ膨隆し，一見逸脱様になり接合不全を呈し，さらに右心不全が悪化する症例も認められた．左心不全に合併する機能性僧帽弁逆流と同様に，肺高血圧症の機能性三尖弁逆流は右心不全を増悪させ，予後を悪化させる因子と考えられる．

●右房機能

右房機能として，(1)三尖弁閉鎖後の収縮期に静脈還流を貯留するreservoir機能，(2)拡張早期の受動的導管機能，(3)心房収縮期のbooster pump機能がある．肺高血圧症で右室圧上昇・右室肥大が生じ，右室のコンプライアンスが低下し右室拡張能障害が出現すると，右房が拡大し右房駆出率が増大することによる心拍出量を保持する代償機能が生じる．

肺高血圧症が進行し，肺動脈圧上昇による右室負荷の進展および三尖弁逆流の増悪とともに右房圧が上昇する．右房圧が上昇するとともに中心静脈圧の上昇が生じ，全身の静脈系のうっ血および右心不全が出現する．右房圧の上昇は，肺高血圧症の重症度の指標となり予後規定因子となる．

右房圧は，下大静脈径とその呼吸性変動の有無により推定される(**図14**)．下大静脈径は，通常は右房から2cm末梢側の部位で，呼吸性変動の最大径と最小径を計測するのが望ましいといわれている．ASEのガイドラインでは，下大静脈径21mm以下の症例では，50％以上の呼吸性変動ある場合は推定右房圧0～5mmHg，50％未満の呼吸性変動の場合は推定右房圧5～10mmHgとされている．下大静脈径＞21mmの症例では，50％以上の呼吸性変動ある場合は推定右房圧5～10mmHg，50％未満の呼吸性変動の場合は推定右房圧15mmHgとされている．さらに詳細な分類もいくつかあるが，右房圧の推定には下大静脈径のみでなく，呼吸性変動の

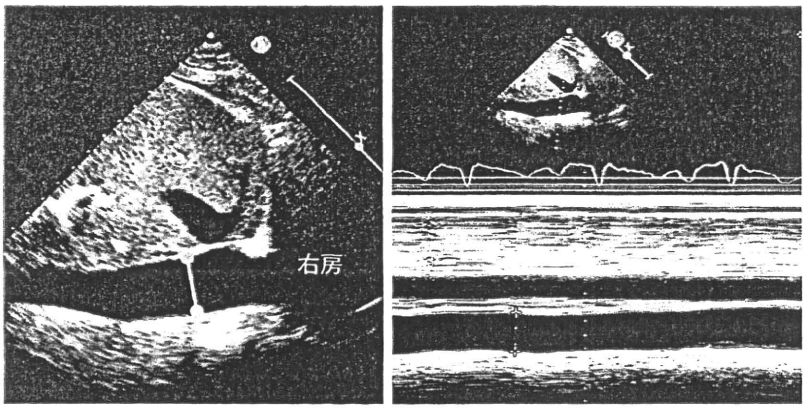


図14　下大静脈の計測
下大静脈径は，右房から2cm末梢の部分で吸気時と呼気時に計測し，呼吸性変動が50％以上あるかも確認し，推定右房圧を算定する．

最大下大静脈径（mm）	呼吸性変動	推定右房圧（mmHg）
≦21	≧50%	0～5
≦21	＜50%	5～10
＞21	≧50%	5～10
＞21	＜50%	15
右室流入血流波が restrictive filling pattern，三尖弁 E/E'＞6，肝静脈の拡張期血流が優位		15

有無が重要であるといわれている．

さらに，肺高血圧症で慢性的に右房負荷が続くと，右室の拡大とともに右房も拡大し，右心不全が出現する症例では，右房・下大静脈の拡大が認められる．JAMP Studyによる日本人の報告としては，右房長軸径は男性45±6mm（右房長軸径/体表面積：26±3mm/m^2），女性42±6mm（右房長軸径/体表面積：28±4mm/m^2），右房短軸径は男性34±5mm（右房短軸径/体表面積：20±3mm/m^2），女性31±5mm（右房短軸径/体表面積：21±3mm/m^2）が正常範囲と報告されている（表5）[5]．ASEのガイドラインでは，右房径および面積は心尖部四腔断層像より計測し，拡張末期の右房面積＞18 cm^2，右房長軸径＞53mm，右房短軸径＞44mmが右房拡大所見とされている[3]．

左室機能

右室と左室は心室間相互作用を有する．右心不全による心拍出量の低下が左心系の左室前負荷の減少を生じ，体循環系の心拍出量低下に寄与する．また，右室と左室は同じ心膜腔という限られた空間に共存し心室中隔を共有していることから，圧負荷，容量負荷によって拡大した右室は，同じ心膜腔内に存在する左室前負荷の減少により狭小化した左室をさらに狭小化させる．さらに，心室中隔は正常な状態では右室側に凸で，収縮期には左室の中心に向かう運動を示すが，右室負荷状態では拡張期に心室中隔は左室側に圧排されて平坦化あるいは左室側に凸となる．心周期においては奇異性運動や非同期運動を示す．これらにより，左室拡張障害が生じ，心拍出量の減少の一因となることが知られている．心エコー図による検討において，肺高血圧症では肺動脈圧の上昇とともに僧帽弁血流波のE/Aが低下し，それとともに心拍出量が減少することが報告されている[10~12]．また，左室拡張末期容量の減少，心室中隔運動の異常，左室拡張機能障害による心拍出量低下による冠動脈血流の減少や，肺血管抵抗上昇に伴う肺動脈主幹部の拡大により冠動脈左主幹部が圧排されることによる冠動脈血流減少によって心筋虚血を生じ，左室機能障害も出現する症例があるともいわれている．肺高血圧症に合併した心不全は，右心不全が主であるが，心拍出量が低下して血圧低下が起こるような症例では，左室拡張能障害の合併，また，ときに左室収縮能低下も起こる可能性のあることを念頭に検査を行うべきである．

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ORIGINAL ARTICLE
Pulmonary Circulation

A Phase III, Multicenter, Collaborative, Open-Label Clinical Trial of Sildenafil in Japanese Patients With Pulmonary Arterial Hypertension

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Background: There is evidence that phosphodiesterase type-5 is effective for the treatment of pulmonary arterial hypertension (PAH).

Methods and Results: A phase III, multicenter, open-label clinical trial of sildenafil 20 mg t.i.d. was conducted in 21 Japanese patients with PAH to examine its efficacy, safety, and pharmacokinetics. The present trial consisted of a screening period and 12-week treatment. Patients who were enrolled in the present trial increased their 6-min walking distance of administration increased at week 12 by 84.2 m from baseline. Hemodynamic parameters (eg, mean pulmonary artery pressure and pulmonary vascular resistance), Borg dyspnea scores, and plasma brain natriuretic peptide concentrations also improved compared to baseline. Most patients improved or sustained WHO functional class. Seven subjects, who were examined for the pharmacokinetics of sildefanil, showed relatively large interindividual variations in the C_{max}, AUC_{0-8}, $C_{ss,av}$, and C_{trough} of the drug. Any serious adverse events, severe adverse events, and deaths were not observed. Most of events of undeniable causality were mild or moderate in severity. Sildefanil was well tolerated by the subjects.

Conclusions: Sildenafil 20 mg t.i.d. was effective and safe for Japanese patients with PAH. (*Circ J* 2011; **75:** 677–682)

Key Words: Efficacy; Pharmacokinetics; Pulmonary arterial hypertension; Safety; Sildenafil

Pulmonary arterial hypertension (PAH) is a group of pathologies with a poor prognosis that are featured by progressive obliteration of the small pulmonary vascular bed and a progressive increase in pulmonary vascular resistance (PVR), eventually leading to refractory right heart failure and premature death.[1–3] A national prospective registry in the United States[4] has reported that the estimated median survival of patients with primary pulmonary hypertension (PPH) who were untreated following a definite diagnosis was 2.8 years and that the estimated 5-year survival rate was 34%. PAH is diagnosed when a mean pulmonary artery pressure (mPAP) is greater than 25 mmHg at rest.[5] The disease is classified the following into several categories: PAH of unknown etiology (idiopathic or familiar) and PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus (HIV) infections, drugs/toxins, and others.[6] PAH provokes exertional dyspnea, easy fatigability, palpitation, chest pain, syncope, cough, and/or other symptoms and considerably deteriorates quality of life of the patients.

In Japan, PPH is designated for listing in the Specified Disease Treatment Research Program, and in 2004 there were 758 patients with identifiable PPH.[7] The number of patients with PAH, including patients with PAH associated with

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underlying disorders (eg, collagen vascular disease and congenital heart diseases), is estimated to be approximately 6,000 in Japan. Therapeutic drugs for PAH have been used in recent years in addition to treatment with conventional agents (anticoagulants, diuretics, inotropic agents, supplemental oxygen, calcium-channel blockers, vasodilators, antiproliferative agents, and endothelin-receptor antagonists).[8]

New insights have been obtained on the pathogenesis of PAH thorough the action of various enzymes. For instance, Rho-kinase activation was recently found to be involved in the pathogenesis of PAH. The inhibition of Rho-kinase reduces monocrotaline-induced PAH, and the phosphorylation of RhoA and prevention of its translocation to the plasma membrane mediate hypoxia-induced PH. Furthermore, there is direct evidence for Rho-kinase activation in PAH patients.[9–11]

Phosphodiesterase type-5 (PDE-5) is strongly expressed in the lung, and PDE-5 gene expression and activity are increased in chronic PH.[12–14] Based on these findings, the inhibition of PDE-5 has been researched as a mechanism of a new approach to the treatment of PAH. Sildenafil (Viagra®), a potent and highly selective inhibitor of PDE-5 that metabolizes cGMP,[15–18] was approved as a therapeutic drug for male erectile dysfunction. cGMP-specific PDE-5 is abundantly present in the pulmonary vasculature, and sildenafil leads to nitric oxide-mediated vasodilation and decreases PVR.[19,20]

The present study was designed as a small-scale clinical trial to clarify the features of sildenafil as a therapeutic drug for PAH in Japan, and its objective was to examine the efficacy, safety, and pharmacokinetics of sildenafil administered orally to Japanese patients with PAH at the regimen of 20 mg t.i.d. for 12 weeks.

Methods

Between April 2007 and February 2009, the phase III, multicenter, collaborative, open-label clinical trial of sildenafil 20 mg t.i.d. was conducted in 21 Japanese patients with PAH who met all inclusion criteria, who did not fall under any exclusion criterion, and who were enrolled at 8 medical institutions in Japan. The protocol of the present trial was approved by the institutional review board or ethical review board at each institution, and the trial was conducted in accordance with the protocol. All subjects provided written informed consent before their enrollment.

The present clinical trial consisted of the screening period and 12-week treatment period. Throughout the treatment period, one 20-mg tablet of sildenafil citrate was orally administered t.i.d. to each subject at intervals ≥6 h. Subjects visited the hospital 5 times (visit 1 at screening, visit 2 at the onset of administration, visit 3 at week 4 of administration, visit 4 at week 8 of administration, and visit 5 at week 12 of administration or at discontinuation), together with contact by phone at week 1 of administration.

The objectives of the present trial were as follows: 1) to verify the efficacy and safety of sildenafil 20 mg t.i.d. administered orally to Japanese patients with PAH for 12 weeks; and 2) to examine the steady-state pharmacokinetics of sildefanil and its metabolite under these conditions of administration.

The main inclusion criteria were as follows: the male or female patient should be aged ≥16 years, should be diagnosed with PAH, and should have a mean PAP >25 mmHg and a pulmonary capillary wedge pressure (PCWP) <15 mmHg in right heart catheterization at screening or baseline.

Assessment of Efficacy

The primary endpoints for efficacy were as follows: 1) change in 6-min walking distance at week 12 of administration from baseline; and 2) changes in baseline hemodynamic parameters [mean PAP, PVR, and cardiac output (CO)] at week 12 of administration from baseline.

The secondary endpoints for efficacy were as follows: 1) change in baseline 6-min walking distance at week 8 of administration from baseline; 2) changes in baseline WHO functional class at weeks 4, 8, and 12 of administration from baseline; 3) changes in baseline hemodynamic parameters [PAP (systolic and diastolic), systemic blood pressures (systolic, diastolic, and mean), PCWP, right atrial pressure, cardiac index, heart rate, PVR index, systemic vascular resistance, systemic vascular resistance index, arterial oxygen saturation, arterial oxygen tension, mixed venous oxygen saturation, and mixed venous oxygen tension)] at week 12 of administration from baseline; 4) changes in baseline Borg dyspnea scores at weeks 8 and 12 of administration from baseline; and 5) changes in baseline plasma brain natriuretic peptide (BNP) concentration at weeks 4, 8, and 12 of administration from baseline.

Assessment of Pharmacokinetics

Subjects in the present trial were assessed for the plasma concentrations and pharmacokinetic parameters [time to reach maximum concentration (T_{max}), maximum concentration (C_{max}), and area under the curve (AUC_{0-8})] of sildefanil and its metabolite at steady state after sildefanil administration, and for the average plasma concentration at steady state ($C_{ss,av}$) and plasma through concentration (C_{trough}) at the steady state of sildefanil.

Blood for the pharmacokinetic assessment was collected before administration and at 0.5, 1, 1.5, 2, 4, 6, and 8 h after administration on the specified visit days. The pretreated samples of the blood collected were used to measure the plasma concentrations of sildefanil and its metabolite at Covance (Indianapolis, IN, USA) according to the liquid chromatography–tandem mass spectrometry method. The lower limit of quantification was 1.00 ng/ml for both sildenafil and its metabolite.

Assessment of Safety

Subjects in the present trial were assessed for adverse events during history taking, physical examinations, laboratory tests [hematology: hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count, differential white blood count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), and prothrombin time; and blood chemistry (total bilirubin, direct bilirubin, AST, ALT, ALP, γ-GTP, albumin, total protein, BUN, creatinine, sodium, potassium, uric acid, and BNP)], vital signs (blood pressure, pulse rate, and body weight), 12-lead electrocardiography, and ophthalmology (examination, visual acuity, color sense, and funduscopy).

Statistical Analysis

SAS software version 8.2 (SAS Institute Inc; Cary, NC, USA) was used to perform all statistical analyses according to Student's t-test. Full analysis set (FAS) was analyzed for efficacy, and FAS and per protocol set (PPS) were analyzed for primary endpoints. FAS consisted of subjects who received at least 1 dose of sildenafil and who were assessed for efficacy at baseline and after sildefanil administration. A P value of <0.05 was considered statistically significant.

PPS consisted of subjects in FAS who met the following

Table 1. Subject Disposition and Analysis Sets

	No. of subjects
Enrolled	21
Medicated	21
Completed	19
Discontinued	2
Analyzed for efficacy	
Full analysis set	20
Per protocol set	16
Assessed for pharmacokinetics	7
Assessed for safety	21
Adverse events	21
Laboratory tests	20

Table 2. Demographic Characteristics of Subjects and Their Features at Baseline

Background factors	No. of subjects
Gender	
Male	4
Female	17
Age (years)	
<18	0
18–44	9
45–64	10
≥65	2
Mean±SD	47.1±14.7
Minimum to maximum	19–68
Body weight (kg)	
Mean±SD	58.5±10.6
Minimum to maximum	38.1–84.0
WHO functional class	
I	0
II	7
III	14
IV	0

Table 3. Types of PAH and Duration of Disease

	No. of subjects
Idiopathic PAH	
No. of subjects	6
Duration of disease (years)	
Mean	1.46
Minimum to maximum	0.1–4.0
Familiar PAH	
No. of subjects	5
Duration of disease (years)	
Mean	1.15
Minimum to maximum	0.3–4.0
PAH associated with other disorders (eg, collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension, HIV infection, and drugs/toxins)	
No. of subjects	10
Duration of disease (years)	
Mean	3.33
Minimum to maximum	0.1–15.0

PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus.

Table 4. Combination Therapies (Therapeutic Drugs for PAH and Basic Therapeutic Drugs for PAH)

	No. of subjects
No. of subjects	21
Therapeutic drugs for PAH	
Beraprost	9
Basic therapeutic drugs for PAH	
Warfarin	9
Cardiotonic drugs (eg, digoxin)	0
Calcium-channel antagonists	12
Diuretics	21
Oxygen therapy	14

PAH, pulmonary arterial hypertension.

Table 5. Six-minute Walking Distance at Baseline and at Weeks 8 and 12 of Administration, as Well as Its Changes From Baseline in Subjects

Endpoint	Six-minute walking distance (m)	
	Actual value	Change from baseline
Subjects		
Baseline		
No. of assessed subjects	20	–
Mean±SD (95%CI)	326.0±86.2 (285.7, 366.3)	–
Week 8 of administration		
No. of assessed subjects	19	19
Mean±SD (95%CI)	410.2±72.9 (375.0, 445.3)	87.5±75.3* (51.2, 123.8)
Week 12 of administration or discontinuation (LOCF)		
No. of assessed subjects	20	20
Mean±SD (95%CI)	410.2±66.6 (379.0, 441.3)	84.2±74.9* (49.1, 119.2)

CI, confidence interval; LOCF, last observation carried forward.
*P<0.0001.

Table 6. Changes in Hemodynamic Parameters at Baseline and at Week 12 of Administration in Subjects

Hemodynamic parameter	Baseline (n=20)		12 week of administration (LOCF) (n=20)			
	Actual value		Actual value		Changes from baseline	
	Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI
Systolic pulmonary artery pressure (mmHg)	75.3±18.5	66.6, 84.0	72.0±20.9	62.2, 81.7	−3.4±13.4	−9.6, 2.9
Diastolic pulmonary artery pressure (mmHg)	30.1±12.4	24.2, 35.9	26.9±11.9	21.3, 32.5	−3.2±8.3	−7.0, 0.7
Systolic systemic arterial pressure (mmHg)	115.4±17.5	107.2, 123.5	116.1±16.1	108.5, 123.6	0.7±16.5	−7.0, 8.4
Diastolic systemic arterial pressure (mmHg)	68.3±14.8	61.3, 75.2	65.2±14.7	58.3, 72.1	−3.1±9.0	−7.3, 1.2
Mean systemic arterial pressure (mmHg)	88.5±19.0	79.6, 97.4	87.7±18.7	78.9, 96.4	−0.9±12.9	−6.9, 5.2
Pulmonary capillary wedge pressure (mmHg)	8.48±2.48	7.31, 9.64	9.15±3.15	7.68, 10.62	0.68±3.14	−0.79, 2.14
Right atrial pressure (mmHg)	6.6±3.4	5.0, 8.2	6.4±3.6	4.6, 8.1	−0.3±4.4	−2.3, 1.8
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.35±0.78	1.98, 2.71	2.67±0.99	2.20, 3.13	0.32±0.62	0.03, 0.61
Heart rate (beats/min)	73.59±15.05	66.54, 80.63	69.45±15.98	61.97, 76.93	−4.14±7.45	−7.62, −0.65
Pulmonary resistance index (dyne·s/cm^5/m^2)	1,581.31±791.94	1,210.67, 1,951.95	1,199.31±660.73	890.09, 1,508.54	−382.00±491.80	−612.17, −151.83
Systemic vascular resistance (dyne·s/cm^5)	1954.86±945.04	1,512.57, 2,397.16	1,689.09–606.04	1,405.45, 1,972.73	−265.77±785.52	−633.41, 101.86
Systemic vascular resistance index (dyne·s/cm^5/m^2)	3,127.11±1,564.66	2,394.82, 3,859.39	2,717.22±1,027.45	2,236.35, 3,198.08	−409.89±1271.30	−1,004.88, 185.09
Mixed blood oxygen saturation index (%)	65.37±9.74	60.81, 69.93	68.28±5.82	65.56, 71.00	2.91±9.05	−1.33, 7.15
Atrial blood oxygen saturation (%)	92.930±6.877	89.711, 96.149	93.370±3.799	91.592, 95.148	0.440±5.437	−2.104, 2.984
Atrial oxygen tension (mmHg)	74.36±15.63	67.05, 81.67	72.35±12.09	66.69, 78.00	−2.02±11.17	−7.24, 3.21
Mixed venous oxygen tension (mmHg)	36.55±4.33	34.46, 38.64	37.12±2.67*	35.83, 38.40*	0.57±4.35*	−1.53, 2.66*

*n=19.
n, no. of evaluated patients; LOCF, last observation carried forward; SD, standard deviation; CI, confidence interval.

criteria: primary endpoints are assessed; there is no violation of the inclusion and exclusion criteria that could possibly affect primary endpoints; any combination-prohibited drug with possible effects on primary endpoints is not used during the study period; and the medication adherence 80–100%. Summary statistics and 95% confidence intervals for the means were calculated with respect to the actual values of the 6-min walking distance, hemodynamic parameters, Borg dyspnea score, and plasma BNP concentration and to their changes from baseline.

The WinNonlin software version 4.1 (Pharsight Corp.; Mountain View, CA, USA) was used to determine pharmacokinetic parameters of sildenafil and its metabolite according to the noncompartment model method in subjects who did not receive any other therapeutic drug for PAH, who met all inclusion criteria for pharmacokinetic assessment and who did not fall under any exclusion criteria for the assessment. All subjects who received at least 1 dose of sildenafil were assessed for safety.

Results

Subject disposition and analysis sets are shown in Table 1. Twenty-one subjects were enrolled, 2 of whom discontinued the trial. Therefore, 19 subjects completed the trial. Of those who discontinued, 1 showed insufficient efficacy and 1 had an adverse event.

Among 21 subjects who were enrolled, 1 and 5 were excluded from FAS and PPS, respectively. The former patient was excluded due to no postdose measurement of all endpoints for efficacy. The latter patients were excluded from PPS because of the following reasons: 2 subjects violated the inclusion/exclusion criteria; 1 subject was excluded from FAS; 1 subject was not evaluated for primary endpoints; and 1 subject ingested a combination-prohibited drug.

The demographic characteristics of subjects and their features at baseline are shown in Table 2. The percentages of males and females were as follows: 19.0% (4 males) and 81.0% (17 females). Subjects had different baseline WHO functional classes: 7 with class II and 14 with class III.

The types of PAH and duration of disease are shown in Table 3. Among the subjects, 6, 5, 10 were diagnosed with idiopathic PAH, familiar PAH, and PAH associated with underlying disorders, respectively.

Therapeutic drugs for PAH and basic therapeutic drugs for PAH, which were administered in combination with sildenafil during the study period, are shown in Table 4. The major therapeutic drug for PAH, which was used in combination therapies during the study period, was beraprost, and the major basic therapeutic drugs for PAH were diuretics and oxygen therapy. Among the subjects, 9 received beraprost in combination with sildenafil; 12 received sildenafil alone.

Efficacy

The actual values of 6-min walking distance at baseline and at weeks 8 and 12 of administration, as well as changes in 6-min walking distance from baseline are shown in Table 5. At week 8 of administration, 6-min walking distance improved statistically significantly ($P<0.0001$) by 87.5 m from baseline. Therefore, the distance was shown to have improved as much at week 8 of administration as at week 12 of administration. At week 12 of administration, the 6-min walking distance had also improved statistically significantly ($P<0.0001$) by 84.2 m from baseline.

The actual values of hemodynamic parameters (mean PAP,

PVR, and CO) at baseline and week 12 of administration are shown in Table 6. The mean PAP and PVR at week 12 of administration decreased as compared with baseline, and CO increased as compared with baseline. The mean PAP and PVR decreased as compared with baseline, and CO increased as compared with baseline.

Among the subjects, only 1 subject showed deterioration in WHO functional class from class II at baseline to class III at week 12 of administration; 6 subjects improved (5 from class III to class II and 1 from class III to class I). Other 13 subjects sustained their class at baseline.

Hemodynamic parameters other than mPAP, PVR, and CO were also assessed. In the subjects, consequently, the change (mean±SD) in PVR index in last observation carried forward (LOCF) at week 12 of administration from baseline was –382.00±491.80 dyne·s/cm^5/m^2; therefore, PVR decreased. Furthermore, the actual value (mean±SD) of PVR index in the LOCF at week 12 of administration was 1,199.31±660.73 dyne·s/cm^5/m^2.

The changes (mean±SD) in Borgs dyspnea score in the LOCF at weeks 8 and 12 of administration from baseline were –0.84±1.89 and –0.95±1.94, respectively. Therefore, the scores decreased as compared with the baseline value (mean±SD: 3.10±1.45).

Plasma BNP concentrations showed an average decrease of 78.00 pg/ml at week 4 of administration as compared with the baseline value (mean±SD: 216.52±204.70 pg/ml) and also sustained decreases also at weeks 8 and 12 of administration.

Pharmacokinetics

The pharmacokinetics of sildenafil and its metabolite at steady state in the repeated oral administration of 20 mg t.i.d. was examined in 7 subjects. Consequently, the mean T_{max} of sildenafil was approximately 1.1 h after administration. The mean values (coefficients of variation) of C_{max}, AUC_{0-8}, $C_{ss,av}$, and C_{trough} of sildenafil at steady state were 164.88 ng/ml (45.4%), 545.14 ng·h/ml (54.1%), 68.14 ng/ml (54.1%), and 19.608 ng/ml (63.4%), respectively. Therefore, relatively large interindividual variations were observed. Furthermore, sildenafil underwent the first-pass effect and rapidly produced its metabolite, and the mean T_{max} value was approximately 1.6 h after administration. The mean values (coefficients of variation) for C_{max} and AUC_{0-8} of the metabolite were 87.27 ng/ml (35.1%) and 365.85 ng·h/ml (51.0%), respectively.

Safety

There were 36 episodes of undeniable causality in 16 cases (76.2%) among 21 subjects. There were no cases of serious and severe adverse events of undeniable causality. However, 2 subjects temporarily reduced the dose of the drug or discontinued its administration because of adverse events of undeniable causality. The major adverse events of undeniable causality were headache (10 cases, 22.7%) and flushing (8 cases, 18.2%); all the events were mild or moderate.

Therefore, there were no safety concerns about laboratory values, vital signs, and electrocardiographic findings.

Discussion

In the present multicenter, collaborative, open-label trial, PAH patients taking sildenafil showed sustained improvement in the 6-min walking distance at weeks 8 and 12 of administration without any serious adverse events causally related to sildenafil administration.

PAH is considered to be caused by pulmonary endothelial dysfunction, by the imbalance between vasoconstrictive factors such as endothelin and thromboxane, and vasorelaxant factors such as prostacyclin and nitric oxide, followed by pulmonary arterial vasoconstriction, and by the proliferation of the vascular wall including endothelium, smooth muscle and adventitia, resulting in increased resistance of pulmonary blood flow through pulmonary arterioles.[18–20] At present, there are 3 categories of effective drugs for PH which present one of the following pharmacological mechanisms. Endothelin receptor antagonists (eg, bosentan) suppress vasoconstriction induced by a vasoconstrictive factor endothelin, dilate pulmonary arteries, and regresses the proliferation of vascular wall cells.[21] Prostacyclin and nitric oxide–which are secreted from the pulmonary artery endothelium, relax smooth muscle cells, and inhibit the proliferation and promote apoptosis of vascular walls– are depleted in PAH patients. Cyclic adenosine monophosphate stimulated by prostacyclin in smooth muscle cells has a potent vasodilating and antiproliferative ability, and a synthetic prostacyclin, epoprostenol, is the first effective drug in the treatment of PH. Nitric oxide stimulates cGMP, which in turn produces cGMP with potent vasodilating and antiproliferative ability. cGMP is degraded by PDE-5 which has been reported to be increased in PAH.[22] Sildenafil inhibits PDE-5 and increases guanosine monophosphate, and alleviates PH.

Six-minute walking distance is a reliable index of functional capacity in patients with PAH and has been widely used as the primary endpoint in most clinical trials designed for patients with PAH.[23–25] In the present subjects, the 6-min walking distance increased by 87.5 m and 84.2 m at weeks 8 and 12 of administration, respectively; these values were greater than those reported with other therapeutic drugs for PAH [eg, epoprostenol (47 m),[23] bosentan (44 m),[24] and beraprost (63 m)[25]].

The efficacy and safety of sildenafil for PAH patients have been demonstrated in uncontrolled[18–20] and controlled[8,16] clinical trials. The controlled clinical trial with the largest number of patients was the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, in which 278 patients were enrolled; the mean 6-min walk distance and mean PVR significantly increased by 45 m and decreased by 122 dyne·s/cm^5, respectively, as compared with the placebo group.[9] Our study afforded comparable results in efficacy. Safety profiles also were almost equivalent between the SUPER study and ours. Namely, any laboratory changes of clinical concern were not observed in these studies. One patient each in the placebo group and the sildenafil 20 mg group died from right heart failure and from acute embolism and urosepsis, respectively, in the SUPER study in contrast to the present trial in which no deaths occurred. The SUPER study reported 1 serious adverse event of undeniable causality in one patient receiving 20 mg of sildenafil in contrast to none in the present trial. The incidences of headache in the SUPER study and ours were 46.0% and 22.7%, respectively.

Changes in hemodynamic parameters (mean PAP, PVR, and CO) at week 12 of administration improved as compared with baseline and indicated a decrease in the mean PAP and an increase in CO. However, no statistically significant changes were found in systemic arterial pressure and heart rate. Therefore, improvement in CO did not involve increases in systemic artery pressure and heart rate. The improvement in CO was also corroborated by an increase in mixed venous oxygen saturation. Decreases in right atrial pressure, systolic pulmonary arterial pressure, and diastolic pulmonary arterial pressure suggested the overall improvement in right heart

function by the administration of sildenafil. The secondary endpoints–changes in other hemodynamic parameters, changes in Borg dyspnea scores, and changes in plasma BNP concentrations–also improved. These results indicated the efficacy of sildenafil which was orally administered to PAH patients at a regimen of 20 mg t.i.d. for 12 weeks.

Study Limitations

The principal limitation of the present trial is the fact that it was not a double-blind, controlled study, because of ethical considerations. Therefore, the possibility of investigator or selection bias cannot be excluded completely with regard to the endpoints examined, especially functional capacity. Another limitation of the present trial was that it did not enroll any PAH patients with WHO class IV. This has possibly favored the clinical outcomes of enrolled subjects with respect to their background at baseline. Although the number of enrolled subjects was as low as at 21, the present study is the first systematically designed study that provides clinical evidence for the efficacy, safety, and pharmacokinetic profile of sildenafil in Japanese patients with PAH.

Conclusions

Sildenafil 20 mg t.i.d. was effective for patients with PAH through improvements in the 6-min walking distance, hemodynamic parameters, Borg dyspnea scores, and plasma BNP concentration after 12-week oral administration. Furthermore, sildenafil showed relatively large interindividual variations in pharmacokinetic parameters, was well tolerated by the patients, and did not elicit any concerns about safety based on the results from laboratory tests, vital signs, and electrocardiography.

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