図 2　大動脈二尖弁の収縮期長軸像
ドーミングが明らかである．

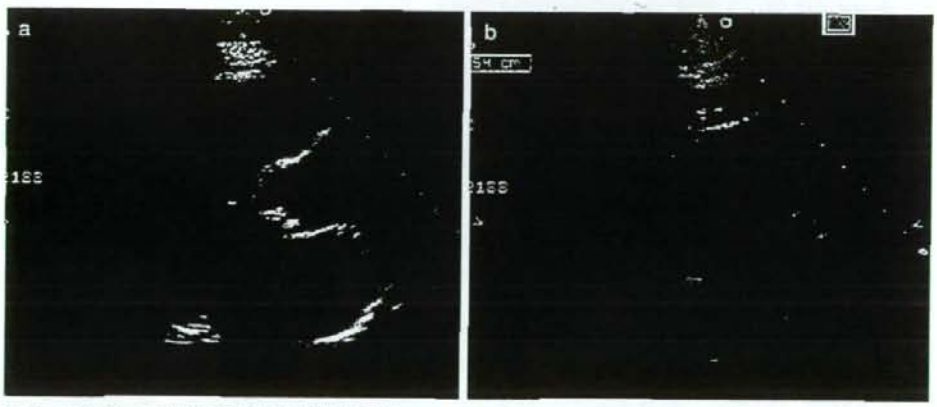

図 3　大動脈二尖弁例における上行大動脈拡大
a：Valsalva 洞直上より拡大が認められる，b：Valsalva 洞遠位部の上行大動脈も軽度拡大している．

の拡大を認める（poststenotic dilatation）．なお二尖弁では狭窄，逆流にかかわらず，大動脈中膜の脆弱化のために上行大動脈拡大のみならず，大動脈瘤，大動脈解離，大動脈縮窄を合併することがあるので可視範囲で大動脈の検索を行う（図 3）．

2）重症度の評価

AS の重症度は連続波ドプラ法により弁通過血流速から算出される最大および平均弁間圧較差，連続の式により求められる弁口面積により評価される（図 4）．弁間圧較差は手軽に求められるが，血行動態の影響を受けるという欠点がある．一方，弁口面積は血行動態の影響を受けないが，計算の過程がやや複雑である．このような欠点を回避するために左室流出路と大動脈弁口での流速の時間速度積分値の比（dimensionless index）を求める方法もある．この比が 0.9～1.0 であれば正常であるが，0.25 以下は高度の狭窄を意味する[2]．

高度 AS の基準については文献によって異なる．わが国のガイドライン[1,3]では弁口面積で 0.75 cm^2 以下または 1 cm^2 以下，弁口面積を体表面積で除した弁口面積係数で 0.6 cm^2/m^2 以下，

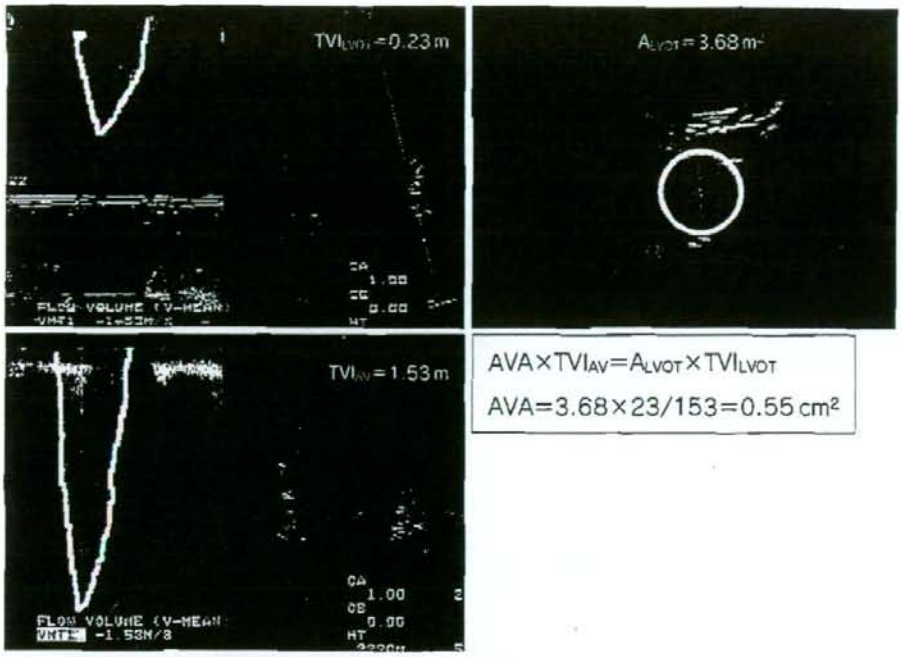

図4 連続の式による大動脈弁弁口面積(AVA)の算出

大動脈弁を通過する血流速の時間速度積分値を TVI_{AV}，左室流出路断面積を A_{LVOT}，左室流出路を通過する血流速の時間速度積分値を TVI_{LVOT} とすると，連続の式より $AVA \times TVI_{AV} = A_{LVOT} \times TVI_{LVOT}$ が成り立つ．本例では TVI_{AV} が 1.53 m，TVI_{LVOT} が 0.23m，A_{LVOT} が 3.68 cm^2 なので AVA は 0.55 cm^2 と計算される．

弁口 dimensionless index 0.25 以下，ドプラ法で記録される弁通過最大血流速度 4 m/s 以上または 4.5 m/s 以上，最大弁間圧較差 64 mmHg 以上または 75 mmHg 以上，平均弁間圧較差 50 mmHg 以上などとされている(表2)．一方，2006年の ACC/AHA のガイドラインでは弁口面積で弁通過最大血流速度 4 m/s 以上，平均圧較差 40 mmHg 以上，弁口面積 1 cm^2 以下，弁口面積を体表面積で除した弁口面積係数で 0.6 cm^2/m^2 以下，とされている(表3)．また左室機能，左室径，肥大の程度，他弁疾患の合併の有無や，三尖弁逆流血流速から肺高血圧の有無についても検索しておく．

左室機能不全を伴った AS では一回拍出量の低下のために弁間圧較差は低値を示し，真の重症度を過小評価する．このような場合には弁口面積による評価が妥当である．なお AS が中等度であっても，何らかの原因による左室機能不全のために一回拍出量がきわめて少ない場合には，駆出血流が弁を十分に押し広げることができず，弁口面積としては小さく計算されることがある．このような例では dobutamine 負荷心エコー法を行って一回拍出量を増大させ，それに伴って弁口面積が増大するかどうかをみるとよい．

3) その他のポイント

狭窄，逆流にかかわらず大動脈弁置換術の際に心エコー検査でみておくべきポイントは，自己弁除去や人工弁縫着の際の障害となりうる弁尖や弁輪の石灰沈着の程度，人工弁サイズを考慮する際に必要な弁輪径，心筋保護を考えるうえで重要な壁肥厚の程度である．上行大動脈が拡大している場合には人工血管による置換が必要となる場合もあるので，大動脈径も計測しておく．

表2　大動脈弁狭窄の重症度

	弁口面積	左室・大動脈圧較差	左室・大動脈平均圧較差
正　常	3～5 cm²		
軽　度	1.1～1.9 cm²	～35 mmHg	～20 mmHg
中等度	0.76～1.0 cm²	36～74 mmHg	21～49 mmHg
高　度	～0.75 cm²	75 mmHg～	50 mmHg～

（日本循環器学会：循環器超音波検査の適応と判読ガイドライン，2005より転載）

表3　大動脈弁狭窄症の重症度（ACC/AHAの指標）

	血流速度 (m/s)	平均圧較差 (mmHg)	弁口面積 (cm²)	弁口面積係数 (cm²/m²)
軽　度	<3.0	<25	1.5<	
中等度	3.0～4.0	25～40	1.0～1.5	
高　度	4.0<	40<	<1.0	<0.6

（Bonow J et al：J Am Coll Cardiol 48：e1-148, 2006）

D　ガイドラインから実践へ

1）手術適応

ASの手術適応に関してACC/AHAが提唱しているガイドラインを図5[2]に示す．日本のガイドラインもこれとほぼ同様であるが[3]，いずれのガイドラインにおいても症状がでるか，心機能が低下し始めている例では手術適応としている．しかし，症状出現の有無は主観的事象であるため外来診療だけでは明瞭でないことも多い．そのような場合にはACC/AHAガイドラインでは運動負荷試験を重視している[2]．なおASに対する運動負荷試験は日本ではいまだ一般的ではないと思われる．症状のない例に対しての運動負荷は実施してもかまわないとされているが，負荷試験を施行する際には血圧と心電図を注意深くモニターしつつ熟練した医師の監視のもとに行われなければならない（表4）[2]．また，加齢に伴うASの治療法は弁置換術をおいて他になく，たとえ高齢であってもASに起因する症状がある例では弁置換術の適応となる．高齢者では冠動脈疾患，脳血管系疾患，腎機能・呼吸機能低下など種々の合併症を有している例が多く，手術に際しては本人，家族の意向なども含めて適応を総合的に判断しなければならない．

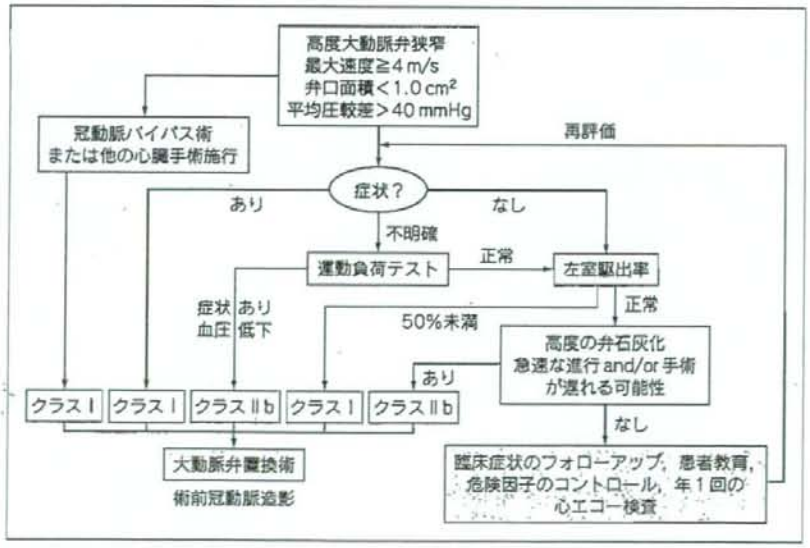

図5　重症大動脈弁狭窄症（AS）の手術適応に関するガイドライン

（Bonow J et al：J Am Coll Cardiol 48：e1-148, 2006）

表4 大動脈弁狭窄症(AS)における運動負荷試験

クラスIIb
無症状の大動脈弁狭窄症例では運動による症状出現や血圧の異常反応をみる目的で運動負荷試験を考慮してよい(エビデンスレベルB)
クラスIII
症状のある大動脈弁狭窄症例には運動負荷試験を行ってはならない(エビデンスレベルB)

エビデンスレベル
A：多施設ランダム化試験のデータに基づく
B：単一施設ランダム化または非ランダム化試験のデータに基づく
C：専門家の一致した意見，症例研究，標準的意見に基づく
(Bonow J et al：J Am Coll Cardiol 48：e1-148, 2006)

2) 重症度の評価

ASの重症度は大動脈弁を通過する血流速度の計測に基づいて評価されるが，低心機能例では一回拍出量が少なくそのため実際の狭窄度のわりに血流速度が遅く計測される可能性がある(過小評価)．またそれとは別に，本来はそれほど重症でないにもかかわらず駆出が小さいために大動脈弁を十分に押し開けることができず，そのため弁口面積として小さく算出される可能性もある(過大評価)．これを偽性大動脈弁狭窄症(pseudo aortic stenosis)と呼んでいる．

このような例に対して，ACC/AHAガイドラインではクラスIIa，日本循環器学会のガイドラインではクラスIIbでdobutamine負荷心エコー検査が推奨されている[1,2]．dobutamine負荷心エコー検査はdobutamineを最大20 μg/kg/minまで静注する．真性のASでは一回拍出量の増加とともに大動脈弁を通過する血流速度が増加し，圧較差が大きく計測される．一方，偽性ASでは一回拍出量を増加させるとそれに応じて弁が押し開けられ弁口面積が増加する．弁口面積が0.2 cm^2以上増加すれば，偽性ASとしてよい．なおdobutamineを最大量投与しても一回拍出量が十分に増えない例(投与前の20%未満)では収縮予備能が低下していることを意味し，収縮予備能が保たれている例に比し予後不良である．

2. 大動脈弁閉鎖不全症

A 病態・症状

1) 病 態

大動脈弁閉鎖不全症(aortic regurgitation：AR)は何らかの原因で大動脈弁尖間の接合が悪くなって逆流が生じる状態である．その原因には，①弁自体の器質的変性のために弁尖の接合が悪くなって生じるものと，②弁尖自体に異常がなくても大動脈基部の拡大に伴って接合が浅くなって生じるもの，の2種類がある．前者にはリウマチ性疾患，二尖弁，四尖弁，加齢に伴うもの以外に感染性心内膜炎や弁尖逸脱などがあり，後者には弁輪拡張症，Marfan症候群，上行大動脈瘤，大動脈解離などがある．

慢性的に高度逆流がある場合には，左室は前負荷・後負荷の増大に適応して肥大を生じ，さらに容量負荷のために徐々に拡大する．これらは壁応力を低下させ，また左室充満圧を増大させないような代償機転であるが，そのうちこれらの代償機転が破綻し心機能が低下する．ここで手術治療のタイミングを逸すると低下した機能の回復は望めない．したがってこのような変化が可逆的であるうちに手術治療を行う必要がある．

感染性心内膜炎や大動脈解離などにより急性に発症したARでは，左室拡張期圧が急速に増大し，しばしば激烈な急性心不全症状を呈し，緊急手術が行われる．

2) 症 状

本症も慢性例では無症状に経過する期間が長い．代償が働かなくなると，労作時息切れ，全身倦怠感で初発し，重症になると起坐呼吸，夜間発作性呼吸困難が出現する．また冠灌流圧の低下や

心肥大に伴う冠動脈予備能低下のために狭心症状を呈することもある．表5にARの自然歴を記す．狭心症状を呈する例では年間10%以上の死亡率，心不全症状を呈する例では年間20%以上の死亡率とされている[2]．急性に閉鎖不全症が起こった例では，急激に激しい左心不全症状で発症する．なおARも感染性心内膜炎の罹患に伴って一気に状態が悪化することがあるので，原因不明の発熱が持続するような場合には早期に来院させ，必要であれば経食道心エコー法を含めた緊急心エコー検査を考慮する．とくに二尖弁によるARの場合には不明熱や，あるいは原因不明の脳梗塞の鑑別疾患として感染性心内膜炎の可能性を考えておかなければならない．

B 心エコー検査の適応(表1)[1]

無症候性であっても聴診上胸骨左縁第3肋間で拡張期逆流性雑音を聴取する場合には精査が必要である．しばしば一回拍出量の増大による駆出性収縮期雑音も聴取する．また頸動脈拍動では二峰性脈と速脈を認める．このような身体所見や前項に述べた臨床症状を示せばARを疑い，心エコー法により診断と重症度評価を行い，また可能な範囲で逆流をきたす病因も明らかにする．

表5 大動脈弁閉鎖不全症(AR)の自然歴

• 左室収縮能が正常な無症候性大動脈弁閉鎖不全症	
症状出現かつ/または左室機能低下	6%/年未満
無症候性左室機能低下	3.5%/年未満
突然死	0.2%/年未満
• 左室機能が低下している無症候性大動脈弁閉鎖不全症	
症状出現	25%/年以上
• 症候性大動脈弁閉鎖不全症	
死亡率	10%/年以上

(Bonow J et al : J Am Coll Cardiol 48 : e1-148, 2006)

C 心エコー判読のポイント

1) 病因の鑑別

a. 短軸像での観察

ARの病因を知るためには断層法で詳細に弁および大動脈を観察する．短軸像は弁尖の数を確認するのによい．二尖弁は若年者のARの代表的病因である．また非常にまれであるが，弁尖が4枚ある四尖弁は中央部にギャップが生じ，そのためASではなくARをきたす(図1，図6)．弁尖が何らかの原因によって一部短縮し，そのため弁尖接合間にギャップが生じる場合もある．その他，器質的異常，輝度増強の有無を観察する．

b. 長軸像での観察

長軸像では弁尖接合の程度を評価し，弁尖接合のズレの有無を観察する(図7)．心室中隔欠損症に伴う右冠尖脱頓によるARでは，心室中隔に右

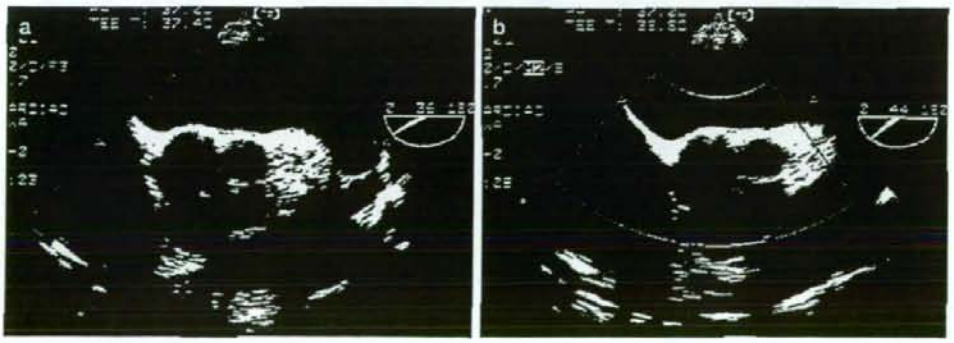

図6 大動脈四尖弁の短軸像
a：断層像，b：カラードプラ像．中央のギャップから逆流ジェットが吹くのがわかる．

冠尖が一部はまりこみ，そのため弁尖接合が不十分になっている像が認められる（図8）．感染性心内膜炎の疣腫は長軸像で観察しやすい．弁尖に器質的異常，輝度増強やズレがなくてもMarfan症候群，大動脈弁輪拡張症のように大動脈弁輪部が拡大している場合には，弁尖に器質的変化がなくても弁尖間中央部にギャップを認め，そこから逆流が生じる（図9）．上行大動脈瘤や大動脈解離でValsalva洞上部が拡大してもやはり弁尖接合が甘くなり中央部から逆流が出現する．したがってARの評価においては心臓・弁のみならず大動脈まで観察することが必要である．なお大動脈解離では弁尖逸脱による逆流をきたすことがある[4]（図10）．

2）重症度の評価

大動脈弁逆流の診断はカラードプラ法により逆流ジェットを検出することにより行われる．重症度の評価はカラードプラ法を用いて求められる逆流ジェットの到達範囲，面積，左室流出路と逆流の幅の比を用いた半定量的評価法，連続波ドプラ法により記録された大動脈弁逆流血流速波形の

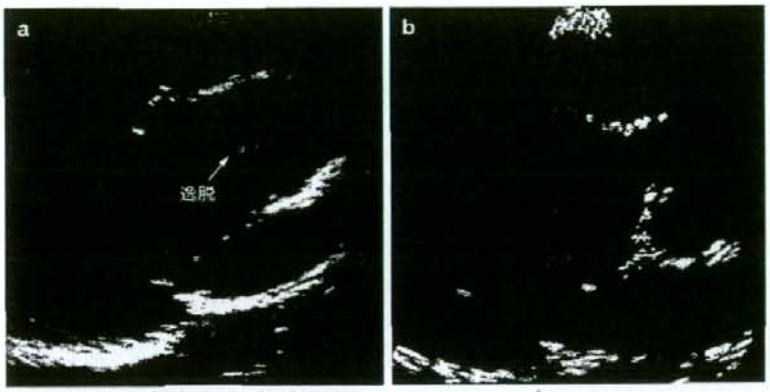

図7 右冠尖の逸脱に伴う大動脈弁逆流
a：断層像，b：カラードプラ像

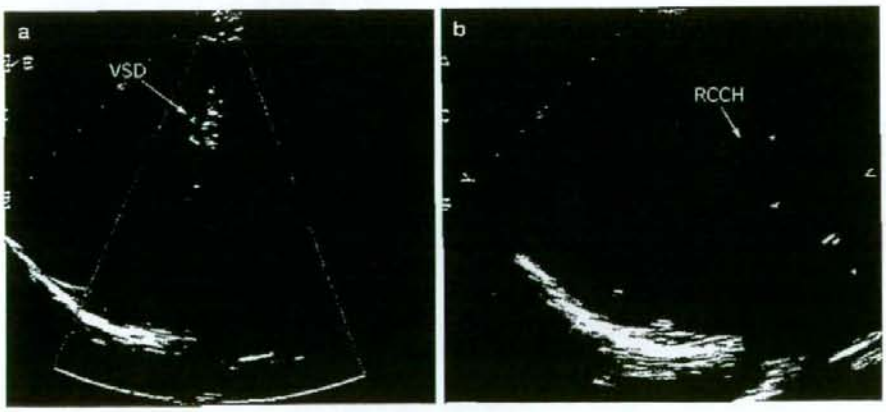

図8 心室中隔欠損症に伴う右冠尖逸脱
a：カラードプラ像，b：断層像．VSD：心室中隔欠損を介するシャント血流．RCCH（right coronary cusp herniation）：右冠尖嵌頓．右冠尖の一部が欠損孔にはまりこんで変形している．

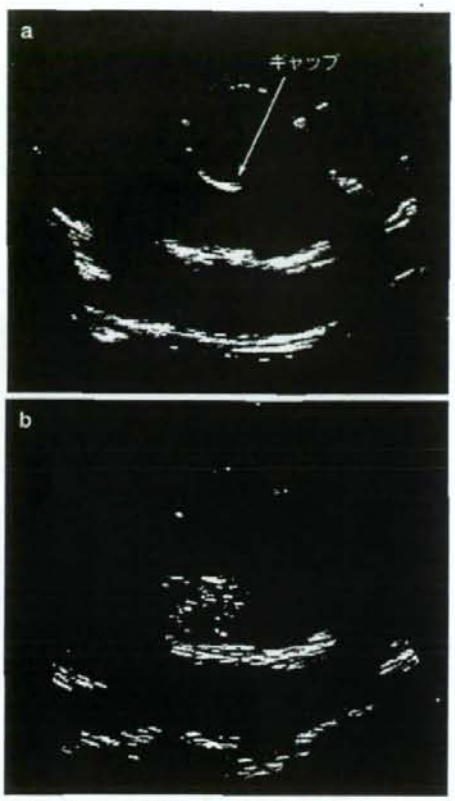

図9　Marfan 症候群における大動脈弁逆流
a：断層像，中央にギャップがある．b：カラードプラ像，ギャップの部位から逆流が吹く．

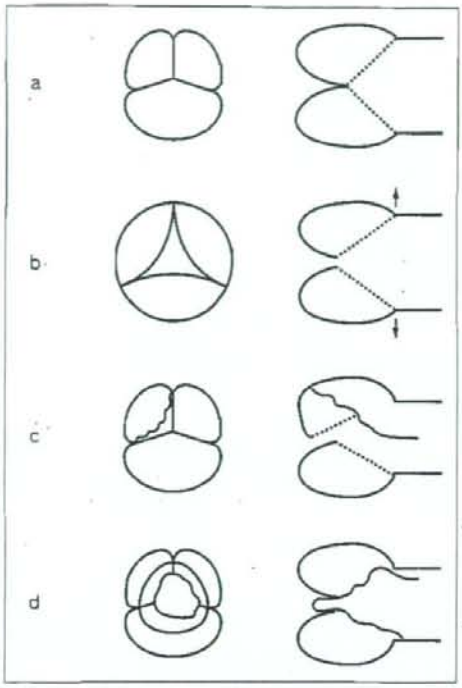

図10　上行大動脈解離の際に大動脈弁閉鎖不全症（AR）が起こる機序
a：正常
b：Valsalva 洞拡大例．弁輪径の拡大がなくても Valsalva 洞上部が拡大すれば弁中央にギャップが生じ逆流を生じうる．
c：解離が大動脈基部にまで及び弁尖の逸脱が生じる．
d：内膜フラップが弁口に嵌頓し閉鎖を障害して逆流が生じる．この場合，通常はフラップの嵌頓のために逆流の持続時間は短い．
（Movsowitz HD et al：J Am Coll Cardiol 36：884-890, 2000）

pressure half-time，ドプラ法を併用した定量的評価法（駆出血流量と左室流入血流量の差による逆流量測定）などによって行う（表6，7）[1]．重症度評価には腹部大動脈の血流速も参考になる．仰臥位で臍部近辺に探触子を当てて記録する．高度の逆流であれば拡張期に反転血流を認める．

表6　大動脈弁逆流の重症度

	左室内到達距離	左室流出路逆流幅比	連続波ドプラ PHT 法
軽　症	流出路内	30% 未満	600 msec 以上
中等症	僧帽弁前尖	30～50%	400～600 msec
重　症	乳頭筋	50～70%	200～400 msec
最重症	心尖部	70% 以上	200 msec 未満

PHT：pressure half-time
（日本循環器学会：循環器超音波検査の適応と判読ガイドライン，2005 より転載）

表 7　大動脈弁閉鎖不全症(AR)の重症度

	軽　症	中等症	重　症
定性評価			
• カラードプラジェット幅	中心流，左室流出路幅の 25% 未満	軽症よりは広いが重症の所見がない	中心流，左室流出路幅の 65% 以上
• vena contracta 幅	<0.3 cm	0.3～0.6 cm	0.6 cm<
定量評価			
• 逆流容量	<30 mL	30～59 mL	60 mL≦
• 逆流率	<30%	30～49%	50%≦
• 逆流弁口面積	<0.10 cm²	0.10～0.29 cm²	0.30 cm²≦
重要な参考事項			
• 左室径			拡大

(Bonow J et al：J Am Coll Cardiol 48：e1-148, 2006)

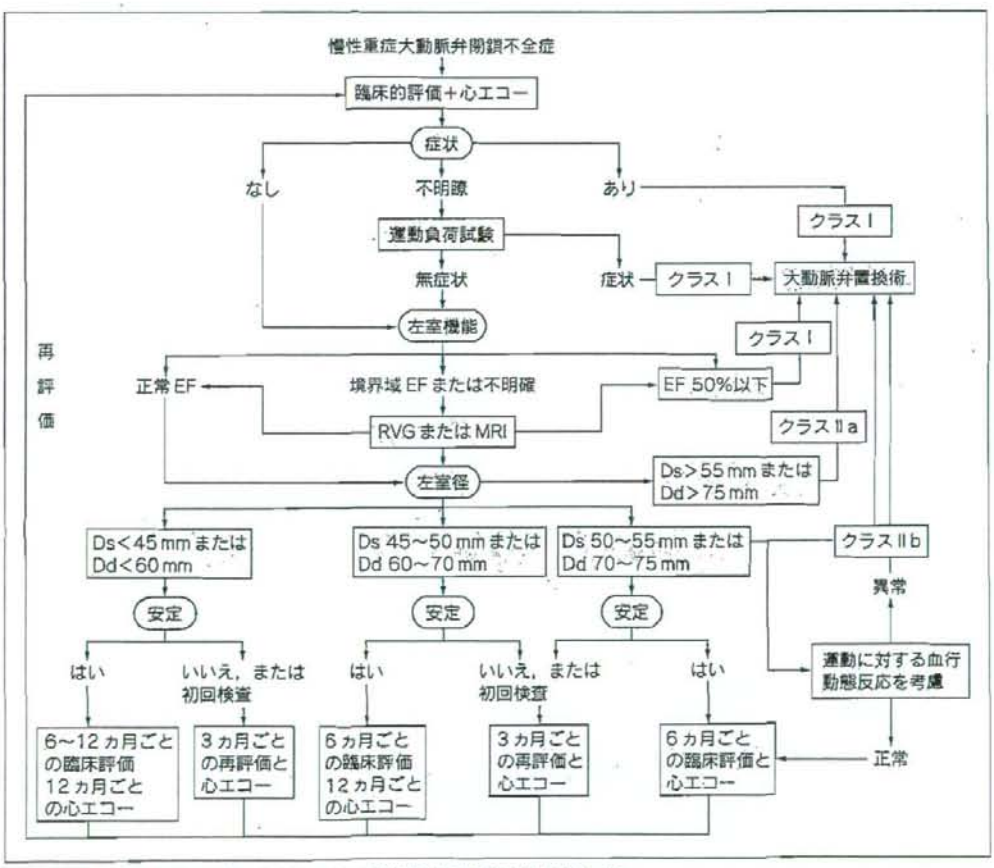

図 11　重症大動脈弁閉鎖不全症(AR)の手術適応に関するガイドライン

RVG：RI 心室造影法，LV：左室径，Dd：左室拡張末期径，Ds：左室収縮末期径

(Bonow J et al：J Am Coll Cardiol 48：e1-148, 2006)

左室径，駆出率は手術適応の基準となる重要な情報であるので[2,3]，前回記録を参照するなどして同じ部位での正確な計測を心がける．心機能，肺高血圧の有無，合併弁膜症の有無をみることは狭窄症と同様である．慢性の大動脈弁逆流では左室は容量負荷により徐々に拡大するが，急性の大動脈弁逆流では左室は急激な容量負荷に耐えきれず高度の肺うっ血を呈するものの，拡大は顕著ではない．またこの場合カラードプラ法による逆流ジェットも，左室内圧の上昇に伴う逆流の駆動圧低下に伴って実際の重症度を過小評価することがある．

D ガイドラインから実践へ

ARの手術適応に関してACC/AHAが提唱しているガイドラインを図11に示す[2]．日本のガイドラインもこれとほぼ同様である[3]．症状のある例，無症状でも安静時の左室収縮機能が低下している例，左室が著明に拡大している例，または大動脈基部が高度に拡大している例が手術適応となる．二尖弁例では大動脈が拡大している可能性を考慮しなければならないが，その際の大動脈径に応じて大動脈基部の形成または上行大動脈置換術の適応を考える．二尖弁でかつ大動脈基部から上行大動脈の径が4 cmを超える例では，毎年径の変化をチェックすべきである（クラスI）[2]．径が5 cmを超えるか，または年間拡大率が0.5 cm/年を上回るようであれば，弁病変にかかわらず大動脈形成術か置換術が必要である．また二尖弁に対して弁置換を行う際に，大動脈基部ないしは上行大動脈径が4.5 cmを超えていれば同時に大動脈形成術か置換術を行ったほうがよい（クラスI）[2]．

文 献

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重要なエビデンス

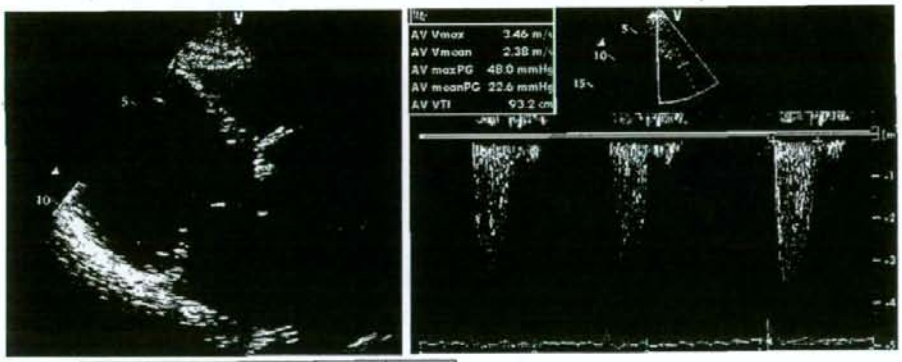
圧較差の低い大動脈弁狭窄症（AS）において術前収縮予備能が術後駆出率に与える影響

(Quere JP et al：Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. Circulation 113：1738-1744, 2006)

圧較差の低い高度ASにおいてdobutamine負荷心エコーを用いて評価される収縮予備能が不良な例は，術後予後が不良であることは知られている．術前収縮予備能と術後駆出率との関係について，大動脈弁置換術を受けた66例の低心機能症候性高度AS（弁口面積≦1.0 cm^2，駆出率≦40%，平均弁間圧較差≦40 mmHg）を対象として検討した．術前dobutamine負荷心エコーの結果，収縮予備能良好例は46例，不良群は20例であった．左室駆出率は全体で29±6%から47±11%に増加した．収縮予備能良好群の38例（83%），不良群の13例（65%）で駆出率が10%以上増加したが，駆出率の増加度は収縮予備能良好群19±10%，不良群17±11%で両群間に差がなかった（p=0.54）．収縮予備能不良例でも術後駆出率が改善する例がある．したがって予備能不良との理由で大動脈弁置換術を見送るべきではない．

ケースアプローチ

■75歳，男性
■主訴：労作時息切れ
■既往歴：胸腹部大動脈瘤術後，陳旧性脳梗塞，慢性閉塞性肺疾患
■現病歴：約10年前に心雑音を指摘された．2年前より労作時息切れ出現．近医で大動脈弁狭窄症（AS）を指摘されたが放置していた．4日前の旅行を契機に体重増加と浮腫出現，昨日より呼吸困難増強したため救急受診，心不全の診断下に入院となった．利尿薬で心不全軽快後，ASの重症度について精査．
■心エコー：左室拡張末期径48 mm，収縮末期径38 mm，心室中隔壁厚12 mm，後壁厚12 mm，大動脈弁口面積0.80 cm^2，弁間平均圧較差25 mmHg
■弁口面積のわりに弁間平均圧較差が小さく，低心機能の関与が疑われたためdobutamine負荷心エコーを実施した（図）．
■dobutamine負荷心エコー：負荷前の大動脈弁口面積は0.77 cm^2であったが，dobutamine 20 $\mu g/kg/min$負荷時の弁口面積は1.16 cm^2と有意（0.20 cm^2以上）に開大した．
■以上より，本例は偽性ASと考えられた．種々合併症のために手術リスクも高く，本人，家族の希望も入れて引き続き内科的治療を継続することになった．



	rest	5γ	10γ	20γ
Peak PG (mmHg)	48	49	64	51
Mean PG (mmHg)	23	26	31	23
AVA (cm^2)	0.77	0.91	0.88	1.16

図 dobutamine負荷心エコー

Circ J 2008; **72:** 1265–1269

Clinical Implication of Energy Loss Coefficient in Patients With Severe Aortic Stenosis Diagnosed by Doppler Echocardiography

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Background The Doppler-derived energy loss coefficient (ELCo), which can take into account the pressure recovery phenomenon and reconcile discrepancies between the aortic valve effective orifice area (EOA) obtained by the Gorlin formula using a catheter (EOA_{cath}) and the EOA obtained by the Doppler continuity equation (EOA_{Dop}), is proposed as an equivalent index to represent EOA_{cath}. Therefore, the purpose of this study was to evaluate the clinical impact of ELCo in patients with severe aortic stenosis (AS).

Methods and Results Thirty-three patients with severe AS were assessed by Doppler examination [EOA obtained by the continuity equation (EOA_{Dop}) $\leq 1.0\,cm^2$], and referred to the cardiac catheterization laboratory for evaluation of EOA obtained by the Gorlin formula (EOA_{cath}). Patients with ELCo $\leq 1.0\,cm^2$ (n=26) had significantly lower incidence of symptoms related to AS compared with those having ELCo $>1.0\,cm^2$ (n=7) (p=0.002). Superior concordance in severity of AS was demonstrated between EOA_{cath} and ELCo compared with EOA_{cath} and EOA_{Dop} (κ=0.52, and κ=0.32, respectively).

Conclusions In 21% of patients with "severe" AS diagnosed by Doppler echocardiography, the ELCo value indicated moderate rather than severe AS. These patients had significantly lower incidence of symptoms compared with patients who had ELCo $\leq 1.0\,cm^2$. (*Circ J* 2008; **72:** 1265–1269)

Key Words: Catheterization; Diagnosis; Echocardiography; Valvular diseases

According to the American College of Cardiology/American Heart Association (ACC/AHA) recommendations, the aortic valve effective orifice area (EOA) can be used to grade aortic stenosis (AS) as severe at $\leq 1.0\,cm^2$.[1] In the clinical situation, the EOA is routinely obtained by using either the Gorlin formula (EOA_{cath}) during cardiac catheterization or the continuity equation (EOA_{Dop}) during Doppler echocardiography[2–5] However, discrepancies between EOA_{cath} and EOA_{Dop} in the grading of the severity of AS, mainly because of the pressure recovery phenomenon, are sometimes observed. The concept of the pressure recovery phenomenon is based on fluid mechanics theory: increased static pressure downstream of the stenosis because of reconversion of kinetic energy into potential energy[6–8] Recently, the Doppler-derived energy loss coefficient (ELCo), which can take into account the pressure recovery phenomenon and reconcile discrepancies between EOA_{cath} and EOA_{Dop}, was proposed as an equivalent index to represent EOA_{cath}[9,10] However, the impact of using ELCo in patients with AS has not been clarified, so the purpose of this study was to evaluate the clinical use of ELCo in patients with severe AS.

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Methods

Patients

We enrolled a total of 33 patients (mean age 71±8 years; females 20, males 13) with severe AS by Doppler examination ($EOA_{Dop} \leq 1.0\,cm^2$), who were referred to the cardiac catheterization laboratory for evaluation of AS. Critical AS is considered to be present when EOA or ELCo is $<0.75\,cm^2$, severe AS when EOA or ELCo is 0.75–1.0 cm^2, and moderate AS when EOA or ELCo is $>1.0\,cm^2$. All patients were in sinus rhythm. We excluded patients with atrial fibrillation, other moderate to severe valvular heart diseases, dialysis and systolic left ventricular (LV) dysfunction (LV ejection fraction <40%). The study protocol was approved by the Ethics Committee of Kawasaki Medical School, and written informed consent was given by all patients.

Table 1 Patients' Characteristics

	Group A (n=26)	*Group B (n=7)*	*p value*
Age (years)	71±8	69±6	0.455
Female sex, n (%)	15 (58)	5 (71)	0.419
Body surface area (m^2)	1.49±0.18	1.42±0.03	0.297
Hypertension (%)	9 (35)	4 (57)	0.281
Diabetes mellitus (%)	6 (23)	1 (14)	0.531
Hyperlipidemia (%)	6 (23)	1 (14)	0.531
Smoking (%)	2 (8)	0 (0)	0.616
Symptoms (dyspnea/angina pectoris/syncope), n (%)	21 (81)	1 (14)	0.002

Table 2 Hemodynamic and Echocardiographic Data

	Group A (n=26)	Group B (n=7)	p value
Hemodynamic data			
LV maximum pressure (mmHg)	197±34	191±25	0.659
LV end-diastolic pressure (mmHg)	20±6	19±5	0.698
Ascending aorta maximum pressure (mmHg)	140±25	161±31	0.061
Ascending aorta minimum pressure (mmHg)	65±12	66±13	0.836
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.0±0.9	3.8±1.3	0.107
Pulmonary capillary wedge pressure (mmHg)	13±6	12±3	0.804
Pulmonary artery maximum pressure (mmHg)	32±12	33±9	0.915
Pulmonary artery minimum pressure (mmHg)	15±7	14±3	0.815
Echocardiographic data			
LV diastolic dimension (mm)	44±6	42±6	0.628
LV systolic dimension (mm)	28±7	27±6	0.888
LV mass index (g/m^2)	195±73	180±51	0.626
LV ejection fraction (%)	64±9	61±8	0.445
Aortic cross-sectional area (mm^2)	58±15	55±8	0.631

LV, left ventricular.

Table 3 Comparison of Medications

	Group A (n=26)	Group B (n=7)	p value
ACE-inhibitors	1 (4%)	0 (0%)	0.787
AT1-receptor antagonists	5 (19%)	2 (29%)	0.469
Calcium-channel blockers	7 (27%)	2 (29%)	0.635
α-blockers	1 (4%)	0 (0%)	0.789
β-blockers	0 (0%)	0 (0%)	1.000
Statins	9 (35%)	1 (14%)	0.294

ACE, angiotensin-converting enzyme; AT1, angiotensin II type 1.

Table 4 Severity of Aortic Stenosis

	Group A (n=26)	Group B (n=7)	p value
Hemodynamic data			
EOA_{cath} (cm^2)	0.70±0.19	1.13±0.32	<0.001
Peak-to-peak gradient (mmHg)	57±29	27±15	0.019
Echocardiographic data			
EOA_{Dop} (cm^2)	0.63±0.13	0.92±0.05	<0.001
ELCo (cm^2)	0.72±0.16	1.11±0.07	<0.001
Maximum transvalvular aortic gradient (mmHg)			
	85±21	52±25	0.003

EOA_{cath}, catheter-derived effective orifice area; EOA_{Dop}, Doppler-derived effective orifice area; ELCo, energy loss coefficient.

Cardiac Catheterization

Cardiac catheterization was performed within 10 days of an echocardiographic examination by 2 experienced cardiologists who were unaware of the echocardiographic data. A standard procedure of catheterization was performed via the femoral approach in all patients, including coronary angiography and pressure measurements. The left ventricle could be reached by retrograde advancement of a 5Fr fluid-filled pigtail side-hole catheter. When direct crossing of the aortic valve was not possible with the pigtail catheter, a right Judkins catheter was used to cross the valve. After recording the LV pressure, the catheter was pulled back into the ascending aorta. The peak-to-peak gradient was measured as: LV maximum pressure−ascending aorta maximum pressure, and the EOA_{cath} was determined according to the Gorlin formula, using 44.3 as the coefficient[7] A 6Fr Swan-Ganz catheter was positioned in the pulmonary arteries. Cardiac output was measured by thermodilution, and the pulmonary capillary wedge pressure was also measured.

Echocardiography

All echocardiographic procedures were performed by 3 experienced cardiologists and 2 sonographers. The transvalvular gradients were measured using a continuous wave Doppler technique, and the EOA_{Dop} was computed with the continuity equation, by measuring the area of the LV outflow tract, and the velocity−time integral in the outflow tract and in the vena contracta[4,5] The diameters of the tubular ascending aorta were recorded in the parasternal long-axis view. In order to correct the EOA for the pressure recovery phenomenon, the ELCo equation was used as previously reported: ELCo = (EOA_{Dop} × aortic cross-sectional area)/(aortic cross-sectional area − EOA_{Dop})[9–11] Study patients were grouped according to the ELCo value: Group A (26 patients with ELCo ≤1.0 cm^2) and Group B (7 patients with ELCo >1.0 cm^2). Symptoms related to AS (chest pain, syncope, and dyspnea), hemodynamic and echocardiographic data were compared between the 2 groups.

Statistical Methods

Continuous variables are reported as mean±SD. Unpaired Student's t-test was used to differentiate between 2 sets of data with normal distribution. If normality tests failed, the Mann-Whitney U-test was used. Comparison of the incidence of symptoms and coronary risk factors was performed using Fisher's exact test. Comparison of each parameter was made using linear regression and the Bland-Altman test[12] Agreement in the assessment of severity of AS between EOA_{cath}, EOA_{Dop}, and ELCo was quantified by the κ test of concordance[13] A p-value <0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the 2 groups; age, gender, and coronary risk factors were similar. Patients in Group B had a significantly lower incidence of symptoms related to AS compared with Group A (p=0.002). The results of hemodynamic and echocardiographic investigtions are summarized in Table 2. There was no significant difference between the 2 groups for medications (Table 3). Table 4 shows the severity of AS assessed by both cardiac catheterization and echocardiography. As expected, EOA was significantly smaller and the pressure gradient was significantly

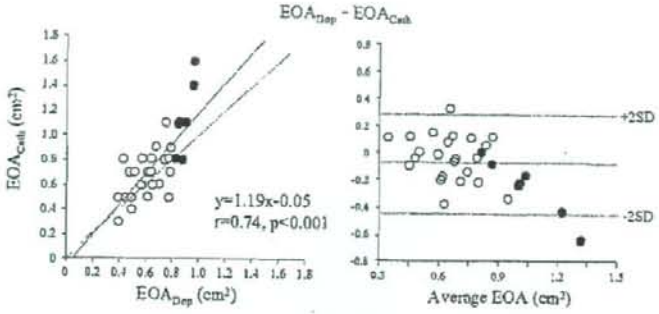

Fig 1. Comparison of the effective orifice area (EOA) measured by a catheter (EOA_{Cath}) vs EOA measured by Doppler echocardiography (EOA_{Dop}) (Left) and the Bland-Altman test for EOA_{Cath} vs EOA_{Dop} (Right). (●) Patients with ELCo >1.0 cm².

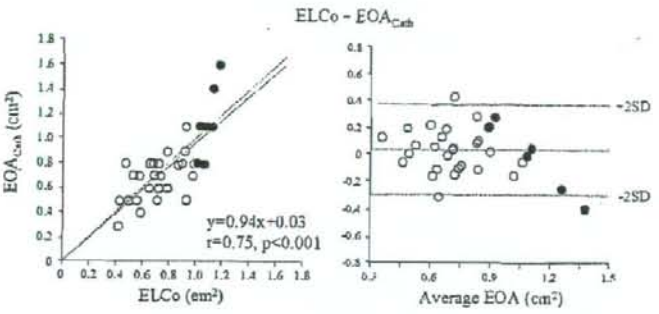

Fig 2. Comparison of the effective orifice area (EOA) measured by a catheter (EOA_{Cath}) vs energy loss coefficient (ELCo) (Left) and the Bland-Altman test for EOA_{Cath} vs ELCo (Right). (○) Patients with ELCo ≤1.0 cm², (●) patients with ELCo >1.0 cm².

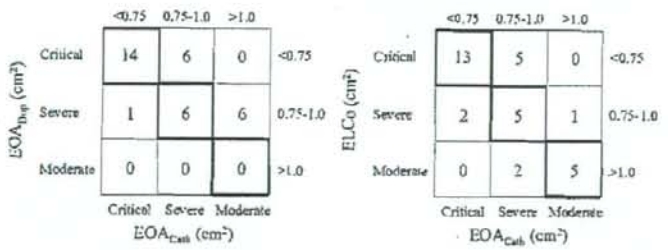

Fig 3. Matrix showing overall severity agreement between effective orifice area (EOA) measured by catheter (EOA_{Cath}) and EOA measured by Doppler echocardiography (EOA_{Dop}) (Left), and EOA_{Cath} and the energy loss coefficient (ELCo) (Right). Critical aortic stenosis is considered present when EOA or ELCo is <0.75 cm², severe aortic stenosis when EOA or ELCo is 0.75–1.0 cm², and moderate aortic stenosis when EOA or ELCo is >1.0 cm².

greater in Group A than in Group B. There was a significant correlation between EOA_{Dop} and EOA_{Cath}, and the Bland-Altman test showed good agreement between EOA_{Dop} and EOA_{Cath} (mean difference, 0.08±0.19 cm²) (Fig 1). Six of the 33 patients (18%) had EOA_{Cath} >1.0 cm². There was a significant correlation between EOA_{Cath} and ELCo, and the Bland-Altman test showed good agreement between EOA_{Cath} and ELCo (mean difference: 0.02±0.18 cm²) (Fig 2). There was a better 1-to-1 correspondence between EOA_{Cath} and ELCo than between EOA_{Dop} and EOA_{Cath} (y=0.94x+0.03 and y=1.19x−0.05, respectively). Seven of the 33 patients (21%) had ELCo >1.0 cm². Superior concordance was demonstrated between EOA_{Cath} and ELCo compared with EOA_{Cath} and EOA_{Dop} (κ=0.52, and κ=0.32, respectively) (Fig 3).

Discussion

In this study, 6 of 33 patients (18%) with "severe" AS by EOA_{Dop} had EOA_{Cath} >1.0 cm², which was classified as moderate AS by the ACC/AHA guidelines. This discrepancy between EOA_{Cath} and EOA_{Dop} is thought to be related to the pressure recovery phenomenon[6–8] ELCo, which can take into account the pressure recovery phenomenon, is proposed as an equivalent index representing EOA_{Cath}, and in this study patients with ELCo >1.0 cm² (21%) had a significantly lower incidence of symptoms related to AS and a lower transvalvular aortic gradient. To the best of our knowledge, this is the first evaluation of the clinical impact of ELCo in patients with "severe" AS diagnosed by the continuity equation.

The ACC/AHA guidelines for defining AS severity are mainly based on data obtained from catheter measurements, as well as clinical outcomes in relation to those measurements[1,14–16] The same value for severe AS (<1.0 cm²) was extended to echocardiographic data on the assumption that EOA_{Dop} and EOA_{Cath} were equivalent parameters, and the aforementioned guidelines do not distinguish between catheter and Doppler measurements. However, it has been reported that discrepancies of up to 20% between EOA_{Dop}

and EOA_{cath} can occur, depending on the pressure recovery phenomenon[9,10] Therefore, measurements made from EOA_{Dop} might result in overestimations of the severity of AS compared with EOA_{cath}, affecting clinical management. On the other hand, there is a strong linear correlation between ELCo and EOA_{cath} compared between EOA_{Dop} and EOA_{cath}. ELCo might be a more exact assessment of AS severity than EOA_{Dop}. In addition, ELCo can be calculated non-invasively from the echocardiogram. Therefore, ELCo might be more appropriate for quantifying AS severity.

The ratio of EOA to the ascending aorta cross-sectional area is a major determinant of the pressure recovery phenomenon[17–19] For example, patients with EOA_{Dop} of 0.9 cm^2 and ascending aorta diameter <3.39 cm would have an ELCo >1 cm^2, shifting the patient's severity from severe to moderate. Similarly, a patient with EOA_{Dop} of 0.8 cm^2 and ascending aorta diameter <2.26 cm would have an ELCo >1 cm^2. Therefore, in patients with severe AS who have EOA_{Dop} of approximately 1.0 cm^2, the evaluation of ELCo, taking into account pressure recovery, is necessary for the assessment of AS severity.

Kadem et al[20] determined the effect of systemic arterial hypertension, induced by banding the distal thoracic aorta in 14 pigs, on the indices of AS severity, including ELCo. They reported that the changes in systemic arterial hemodynamic properties associated with systemic hypertension could cause a decrease in the mean flow rate and thus an increase in ELCo. In the present study, the ascending aorta maximum pressure was greater in Group B than in Group A, although the difference was not statistically significant, but may have affected the ELCo value in this study. On the other hand, hypotension associated with LV dysfunction could cause a decrease in ELCo. Measuring AS severity by calculating ELCo is recommended/should be performed when the patient is normotensive.

Study Limitations

Pressure recovery was not directly measured by invasive technique and usage of standard protocols meant that distal pressure measurements were not obtained at sites where pressure had recovered to the fullest extent. Theoretically, the distance required for full pressure recovery depends on the orifice size and aortic diameter[6,7] However, previous in vitro studies have shown that most pressure recovery occurs within several centimeters and that differences between wall measurements at 5 cm and central measurements at 10–20 cm downstream from the stenosis are small and clinically irrelevant[18,21–23] The distance for the occurrence of pressure recovery increases with the diameter of the aorta, whereas a large diameter aorta precludes clinically significant pressure recovery. In addition, clinical study suggests that all measurable increase of pressure occurs within the ascending aorta[24,25] Therefore, the measurement technique used in this study should reflect pressure recovery to a great extent.

Our study has the inherent limitations of any small, observational series and further large-scale studies are needed to reveal the clinical implications of using ELCo in patients with AS.

Conclusions

In 21% of patients with "severe" AS diagnosed by Doppler echocardiography, the ELCo value indicated moderate rather than severe AS (>1.0 cm^2). These patients had a significantly lower incidence of symptoms related to AS than patients who had ELCo ≤1.0 cm^2. ELCo, which can be calculated non-invasively from the echocardiogram, might be a useful measure for quantifying the severity of AS.

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C-Reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis

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Background C-Reactive protein (CRP) has been shown to play a pivotal role in the pathogenesis of atherosclerosis progression. The aim of this study was to assess whether CRP predicts severity, progression, and prognosis of aortic valve stenosis (AS).

Methods One hundred and thirty-five patients with asymptomatic AS were studied. Patients were diagnosed as mild (n = 18, aortic valve area [AVA] ≥1.5 cm^2), moderate (n = 57, AVA 1.0-1.49 cm^2), or severe AS (n = 60, AVA <1.0 cm^2) by Doppler echocardiography. Patients with serial (baseline and at 1 year) echocardiographic examination (n = 47) were grouped as either slow (n = 22, ΔAVA <–0.15 cm^2/y) or rapid progression group (n = 25, ΔAVA ≥–0.15 cm^2/y). In addition, long-term prognosis was compared between patients with low CRP (n = 68, CRP <0.15 mg/dL) and those with high CRP (n = 67, CRP ≥0.15 mg/dL).

Results Baseline CRP was significantly higher in patients with severe AS than in those with mild or moderate AS (mild AS 0.17 ± 0.43, moderate AS 0.22 ± 0.28, severe AS 0.53 ± 0.66 mg/dL, $P = .001$). By multivariate logistic regression analysis, CRP was an independent predictor of severe AS (odds ratio 3.51, $P = .015$). Similarly, CRP was significantly higher in the rapid progression group than in the slow progression group (0.56 ± 0.76 vs 0.19 ± 0.25 mg/dL, $P = .004$). Furthermore, long-term survival was significantly lower in the high CRP group than in the low CRP group (log rank: $P < .001$).

Conclusion C-Reactive protein predicts severity, progression, and prognosis in patients with asymptomatic AS. (Am Heart J 2008;156:713-8.)

In adults older than 65 years, aortic valve stenosis (AS) is seen at a rate of 2% to 3%.[1,2] Aortic valve disease is still the leading cause of cardiac valve replacement in developed countries.[3] Although several investigators have suggested possible predictors of AS, the exact mechanisms of AS remain unclear.

Inflammation is an important etiologic factor of cardiovascular disease.[4] C-Reactive protein (CRP) has been reported as an independent predictor of the atherosclerosis progression. Increased CRP has also been reported in patients with degenerative AS, suggesting that inflammation may play a pathogenic role in AS.[5-7] However, the relationship between CRP and severity of AS is unclear. Although CRP may be related to progression of AS, its impact on mortality has not been investigated. The aim of this study was to assess whether CRP predicts severity, progression, and prognosis of AS.

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Methods

The present study included 135 patients who were suspected AS for cardiac murmur and/or echocardiographic routine assessment to our hospital between January 2004 and March 2006. Patients with bicuspid aortic valves (n = 17), history of ischemic heart disease (IHD, n = 18), systemic inflammatory disease (n = 12), hemodialysis (n = 18), and rheumatic valve disease (n = 2) were excluded.

Echocardiographic assessment was carried out with a Sonos 5500 system (Philips Medical Systems, Bothell, WA) using standardized imaging techniques. The peak velocity across the valve was measured with continuous-wave Doppler from whichever window gave the greatest velocity signal. Aortic valve area (AVA) was calculated by the continuity equation.[8,9] Study patients were diagnosed as mild AS (AVA ≥1.5 cm^2), moderate AS (AVA 1.0-1.49 cm^2), and severe AS (AVA <1.0 cm^2). And 47 (35%) of 135 patients who underwent repeat echocardiographic assessment at 1 year later were grouped as slow progression group (n = 22, a decrease in AVA <0.15 cm^2/y) and rapid progression group (n = 25, a decrease in AVA ≥0.15 cm^2). The cut-off of AVA value to separate between rapid and slow progression of AS was defined based on the average from previous reports.[10-12]

In addition, study patients were divided into 2 groups based on baseline median of CRP value in this study: low CRP group

Table I. Clinical characteristics and biochemical findings among the 3 study groups

	Mild AS (n = 18)	Moderate AS (n = 57)	Severe AS (n = 60)	P value
Age (y)	71 ± 10	77 ± 9	78 ± 8	.019
Male sex, n (%)	7 (39)	22 (39)	19 (29)	.700
Hypertension, n (%)	8 (44)	20 (35)	23 (38)	.769
Hyperlipidemia, n (%)	1 (6)	19 (33)	17 (28)	.069
Diabetes mellitus, n (%)	1 (6)	8 (14)	10 (17)	.493
Smoking, n (%)	4 (22)	12 (21)	12 (20)	.977
Total cholesterol (mg/dL)	179 ± 38	184 ± 39	180 ± 40	.910
LDL Cholesterol (mg/dL)	124 ± 15	122 ± 28	121 ± 28	.821
CRP (mg/dL)	0.17 ± 0.43	0.22 ± 0.28	0.53 ± 0.66	.001
Medications				
Statin, n (%)	1 (6)	12 (21)	11 (18)	.321
ACE Inhibitor/ AT1 receptor antagonist, n (%)	3 (17)	18 (32)	18 (30)	.429
β-Blocker, n (%)	3 (17)	2 (4)	1 (2)	.068
Calcium blocker, n (%)	7 (39)	13 (23)	16 (27)	.423
Creatinine (mg/dL)	0.87 ± 0.42	0.86 ± 0.32	0.84 ± 0.26	.906
BMI (%)	22.6 ± 3.7	22.0 ± 3.3	21.6 ± 3.3	.543

LDL, Low-density lipoprotein; AT1, angiotensin II type 1; ACE, angiotensin-converting enzyme; BMI, body mass index.

(n = 68, CRP >0.15 mg/dL) and high CRP group (n = 67, CRP ≥0.15 mg/dL).

Left ventricular (LV) mass was calculated with the Devereux formula.[13] Left ventricular mass index was calculated by dividing LV mass by height in meters raised to the power of 2.7. The degree of calcification of the aortic valve was assessed and scored as mild (no calcification or small isolated calcified spots), moderate (multiple large spots), or severe (extensive thickening and calcification of all the aortic valve cusps).[14]

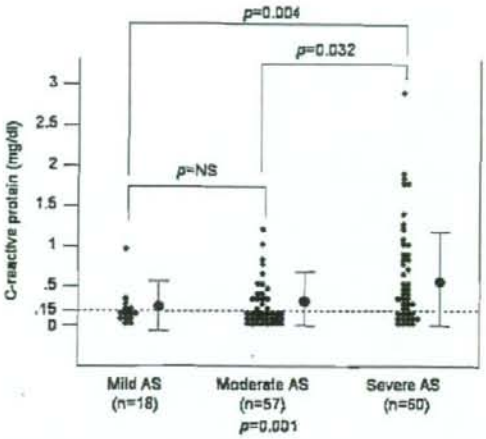
The serum CRP was measured by latex nephelometry (LT Auto Wako CRP, Osaka, Japan). We used latex as the reagent and Hitachi 7500 analyzer (Hitachi, Tokyo, Japan) as the measurement system. The lowest detection CRP limit of this test was <0.02 mg/dL.

Hypertension was defined as a history of systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or the use of antihypertensive therapy. Hyperlipidemia was defined as a fasting total cholesterol concentration of ≥220 mg/dL or the use of antihyperlipidemic therapy. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dL or the use of antidiabetic therapy. Informed consent was obtained from all patients. Study protocol was approved by the Institutional Review Committee on Human Research at our institution.

Clinical follow-up

To further address the prognostic impact of CRP in patients with AS, long-term clinical events were compared between low-CRP and high-CRP groups. Long-term clinical events included death, hospitalization due to congestive heart failure, and aortic valve replacement.

Figure 1



C-Reactive protein level in patients with mild, moderate, and severe AS. C-Reactive protein in patients with severe AS was significantly higher than in patients with mild or moderate AS.

Statistical analysis

Data are expressed as mean value ± SD. The 2 groups were compared with an unpaired Student *t* test and χ^2 test. Statistical comparison between the 3 groups was performed by 1-way analysis of variance and post hoc multiple comparison, using the Scheffé's test. Logistic regression analysis was used to identify the independent risk factor for severity of AS. Long-term survival was evaluated by Kaplan-Meier survival analysis. A *P* value of <.05 was considered significant.

Results

One hundred and thirty-five patients with mild (n = 18), moderate (n = 57), and severe AS (n = 60) were examined in this study. All patients were asymptomatic at the time of baseline echocardiographic study. Table I summarizes the baseline clinical characteristics data of the 3 study groups. There were significant differences in age and CRP among mild, moderate, and severe AS. Figure 1 shows plots of CRP in patients with mild, moderate, and severe AS. C-Reactive protein in patients with severe AS was significantly higher than in patients with mild or moderate AS ($P = .004$ vs mild AS, $P = .0032$ vs moderate AS, respectively). CRP correlated weakly but significantly with AVA ($r = 0.26$, $P = .003$). Table II shows the echocardiographic findings. There were significant differences in LV ejection fraction (LVEF), degree of calcification, and LV mass index among mild, moderate,

Table II. Echocardiographic findings among the 3 study groups

	Mild AS (n = 18)	Moderate AS (n = 57)	Severe AS (n = 60)	P value
LV Diastolic dimension (mm)	43.1 ± 6.4	43.1 ± 5.0	42.2 ± 5.1	.650
LV Systolic dimension (mm)	26.3 ± 5.4	26.1 ± 5.0	26.9 ± 5.9	.697
LV Septal wall thickness (mm)	10.9 ± 1.1	11.9 ± 2.4	12.9 ± 2.2	.002
LV Posterior wall thickness (mm)	10.6 ± 1.5	11.8 ± 2.0	12.6 ± 1.9	<.001
LVEF (%)	68.4 ± 5.6	66.0 ± 7.3	62.2 ± 10.0	.009
Aortic valve area (cm^2)	1.70 ± 0.21	1.18 ± 0.14	0.75 ± 0.16	<.001
Peak aortic velocity (m/s)	2.48 ± 0.40	2.74 ± 0.59	3.90 ± 0.90	<.001
Peak pressure gradient (mm Hg)	25.4 ± 7.8	31.6 ± 14.8	63.8 ± 31.1	<.001
Severe calcification, n (%)	5 (28)	18 (32)	33 (55)	.016
LV Mass index (g/m^2)	125.6 ± 40.3	157.4 ± 50.9	169.7 ± 73.4	.028

EF, Ejection fraction.

Table III. Multivariate analysis of variables associated with severe AS

	OR (95% CI)	P value
CRP	3.51 (1.27-9.71)	.015
LVEF	0.95 (0.90-1.00)	.047
Severe calcification	2.16 (0.99-4.73)	.054
Age	1.02 (0.98-1.07)	.288
LV Mass index	1.00 (0.99-1.00)	.559

OR, Odds ratio.

and severe AS. Valve calcification and LV mass index were also found to be positively associated with the severity of AS ($r = 0.48$, $P < .001$; $r = 0.23$, $P = .006$, respectively). During the follow-up period, 13 patients (10%) (2 patients with moderate AS, 11 patients with severe AS at baseline) developed symptoms and underwent aortic valve replacement. Baseline CRP was similar in patients with moderate and severe AS who developed symptoms (median 0.23 ± 0.25 and 0.33 ± 0.39 mg/dL) compared with those who were asymptomatic (0.21 ± 0.29 and 0.57 ± 0.70 mg/dL, $P = .679$ and .249, respectively). By univariate analysis, CRP ($P = .001$), LVEF ($P = .009$), age ($P = .019$), calcification ($P = .016$), and LV mass index ($P = .028$) were predictors of severe AS. By multivariate analysis, CRP and LVEF were independent predictors of severe AS (Table III).

Table IV presents a summary of the comparison between the rapid progression group and slow progression group. Although clinical and echocardiographic data were similar, baseline CRP was significantly higher in the rapid progression group than in the slow progression group. By univariate and multivariate analysis, CRP was the only independent predictor of rapid progression (odds ratio 1.91, 95% CI 0.861-4.216, $P = .024$).

During follow-up (mean 23 ± 11 months), 33 deaths (23 cardiac deaths and 10 noncardiac deaths), 25 hospitalization due to congestive heart failure, and 13 aortic valve replacements were documented. Kaplan-Meier survival analysis showed that long-term survival as well as event-free survival was significantly lower in the high CRP group than in the low CRP group (Figures 2 and 3).

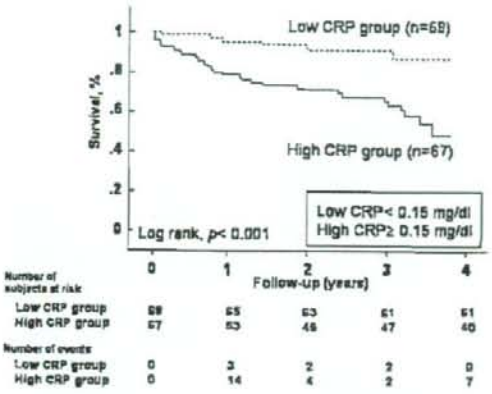
Table IV. Comparison of baseline characteristics of study patients between the rapid progression group and slow progression group

	Rapid progression (n = 25)	Slow progression (n = 22)	P value
Age (y)	75 ± 9	75 ± 8	.482
Male SEX, n (%)	9 (36)	7 (32)	.503
CRP (mg/dL)	0.56 ± 0.76	0.19 ± 0.25	.004
Hypertension, n (%)	7 (28)	11 (50)	.106
Hyperlipidemia, n (%)	9 (36)	8 (36)	.601
Diabetes mellitus, n (%)	6 (24)	2 (9)	.167
Smoking, n (%)	6 (24)	4 (18)	.450
Total cholesterol (mg/dL)	189 ± 39	175 ± 35	.200
LDL Cholesterol (mg/dL)	133 ± 24	124 ± 10	.155
Statins therapy, n (%)	4 (16)	5 (23)	.549
AVA (cm^2)	1.08 ± 0.40	1.02 ± 0.37	.309
Peak aortic velocity (m/s)	3.36 ± 0.87	3.01 ± 0.80	.085
Peak pressure gradient (mm Hg)	47.9 ± 23.9	38.5 ± 20.8	.079
LVEF (%)	65.3 ± 11.1	66.6 ± 6.7	.689
Severe calcification, n (%)	11 (44)	7 (32)	.289
AS Grade, n (%)			
Mild	5 (20)	2 (9)	.265
Moderate	8 (32)	11 (50)	.169
Severe	12 (48)	9 (41)	.424

Discussion

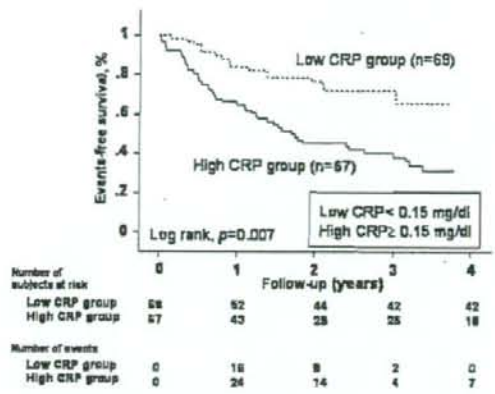
To the best of our knowledge, this is the first study demonstrating that baseline CRP is an independent predictor of severe AS. In addition, serial echocardiographic

Figure 2



Kaplan-Meier plots of all-cause deaths–free survival curves showing a significantly lower survival rate in the high-CRP group than in the low-CRP group.

Figure 3



Kaplan-Meier survival plots of event (cardiac death, noncardiac death, hospitalization due to congestive heart failure, and aortic valve replocement)-free survival curves showing a significantly lower survival rate in the high-CRP group than in the low-CRP group.

examination shows that CRP is associated with progression of AS. Furthermore, CRP is related to long-term clinical outcome in patients with asymptomatic AS.

Histologic findings of AS resemble the morphological changes seen in atherosclerosis including calcification, fibrosis, and lipid storage.[15] Microscopically chronic inflammation characterized by infiltration of T lymphocytes and macrophages and by accumulation of plasma lipoproteins such as oxidized low-density lipoprotein and lipoprotein (a) is detected.[16] Skowasch et al[17] reported that CRP has been localized in the valve tissue of both calcific AS and degenerative aortic valve bioprostheses, with a positive correlation between serum CRP and valvular expression. Therefore, it is possible that inflammation plays an important role during the course of aortic valve sclerosis, calcification, and stenosis. Also, it may be inconclusive whether increased CRP is a cause or result of severe AS based on the difference in CRP among patients with mild, moderate, and severe AS.

Aortic valve stenosis tends to progress overtime, and the rate of progression varies in different patients. Otto et al[10] suggested that AVA decreased by 0.10 to 0.12 cm^2/y, and mean gradient increased by 5 to 10 mm Hg/y in patients with asymptomatic AS. Whereas Kume et al reported that the degree of AS progressed more rapidly in patients undergoing dialysis with severe aortic valve calcification (AVA 0.17 cm^2/y, maximum velocity 0.37 m/s per year, respectively) and older than 80 years with mild to moderate AS (AVA 0.10 cm^2/y, maximum velocity 0.11 m/s per year, respectively).[11,12] Moreover, Beppu et al[18] reported the rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves (maximum pressure gradient 8 mm Hg/y). In this study, CRP was significantly higher in the rapid progression group than in the slow progression group. These results were concordant with a previous study. Sanchez et al[19] reported that CRP is higher in patients with rapid progression of AS. On the other hand, Novaro et al[20] reported that CRP was not associated with progression of aortic sclerosis. Previous reports suggested that aortic sclerosis and AS are considered different stages in the continuum of calcific aortic valve disease.[21,22] Therefore, CRP may not be associated with early stage of this continuum but with advanced stage of AS.

The relationship between progression of AS and statin therapy is still controversial. Previous studies have suggested that cholesterol lowering by statin therapy may have a salutary effect on the progression of AS.[23-27] However, a recent randomized study by Cowell et al[28] showed a negative result. In the present study, statin was prescribed in a small subset of patient and there was no significant difference in statin use between the rapid and slow progression group. Recent studies consistently showed that statin did lower not only low-density lipoprotein cholesterol but also CRP.[29-31] Therefore, statin may be efficacious in patients with AS with elevated CRP.

In our present study, long-term survival was significantly lower in patients with AS with high CRP level. Previous reports suggested that CRP might be a cardiovascular risk marker in patients with IHD, stroke, metabolic syndrome, and renal disease.[5,6,32-35] Although

high CRP may represent the presence of comorbid condition such as IHD, CRP may be a useful parameter to predict disease progression and prognosis in patients with AS.

Study limitations

First, this is a retrospective analysis of a small number of patients from a single center. Thus, the results need to be confirmed by a large prospective multicenter study. Second, although patients with known history of IHD were excluded, it is possible that occult coronary artery disease was related to the elevated CRP. Although previous studies showed that coronary artery disease was detected in 33% and 45% of patients with AS,[36,37] significant coronary artery disease was detected in <10% of the severe AS at our hospital (data not shown). Therefore, it is unlikely that coronary artery disease affects our results. Third, the percentage of females was high in our study. It might be due to the exclusion of patients with bicuspid valves and ischemic heart disease. In fact, the percentage of males was higher than that of females (male 69%, female 31%) among patients with bicuspid valves and ischemic heart disease. However, we did not observe any sex-specific differences in this study.

Conclusion

C-Reactive protein is associated with the severity and progression of asymptomatic AS. In addition, CRP predicts long-term clinical outcome in patients with AS. These findings suggest that CRP may have a pathogenic role and prognostic impact in asymptomatic patients with AS.

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