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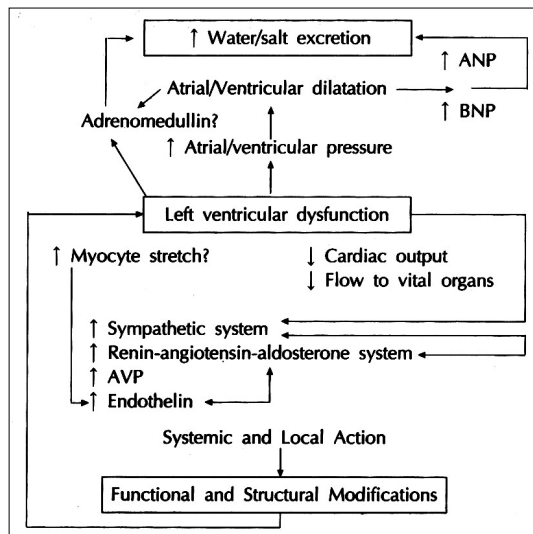


Fig. 1. Activation of neurohormonal system in heart failure.

Table 1. Adverse effects of angiotensin in congestive heart failure

Left ventricular structural and functional effects
Increased transmural wall stress
Dilation caused by increase of end-diastolic and endsystolic volumes
Decreased coronary flow in epicardial and transmural vessels
Hemodynamic effects
Increased vascular resistance
Positive Inotropic stimulation
Neurohormonal and paracrine effects
Increased tissue effects of angiotensin
Stimulation of aldosterone production, with sodium (and volume) retention
Increase of circulatory catecholamines, impaired baroreceptor function, and abnormal
Sympathetic-parasympathetic balance
Increased bradykinin degradation
Stimulate the secretion of arginine vasopressin
Mitogenic and growth effects
Myocardial hypertrophy
Vascular smooth muscle hypertrophy
Cell protein enhancement

가
vicious cycle
1)2)

Renin-Angiotensin-Aldosterone
System (RAAS)

RASS

RAAS가
angiotensin, aldosterone 가

가

renin system

renin system
aldosterone
가 angiotensin
(Table 1).

Angiotensin angiotensin
(Fig. 2).⁴⁾

Angiotensin ACE(ang -
iotensin converting enzyme) bradykinin
bradykinin ACE in -
hibitor angiotensin

bradykinin 가 angiotensin
, bradykinin
vasodilation, antihypertrophic and antiprolifera -
tive effect 가 ⁵⁾⁶⁾ 가

ACE inhibitor

Angiotensin Fig. 2
ACE enzyme ,
non - ACE pathway가

가 angiotensin receptor blocker . RAAS
final product aldosterone myocardial fibrosis
angiotensin 가

aldosterone aldoster -
one antagonist spironolactone

Angiotensin con-verting enzyme (ACE) inhibitor

Trials of ACE inhibitors in patients with CHF (Table 2)

ACE inhibitor
Cooperative North Scandinavian Enalapril
Study (CONSENSUS - 1) ⁷⁾ NYHA

Table 2. Effects of Ace inhibitors in patients with congestive heart failure

Study	No.	Age	CAD	EF	Class	Drugs	F/U	Mortality reduction
CONSENSUS	253	70	74%	N/A		Enalapril	1 88 days	27%(p = 0.003)
V-HeFT	804	61	53%	29%	,	Enalapril	2.5 years	28%(p = 0.002)
SOLVD treat.	2569	61	70%	25%	,	Enalapril	41.1 mos.	16%(p<0.004)
SOLVD prev.	4228	59	83%	28%	,	Enalapril	37.4 mos.	8%(p = 0.30)

class 253 . Enalapril
 placebo 6 26% vs 44%, 1 29% ACE inhibitor가
 36% vs 52%
 가 ACE inhibitor ACE inhibitor
 . NYHA class
 Studies on Left Ventricular Dysfunction
 (SOLVD) Treatment Trial .⁸⁾ 2,569 Evaluation of ACE inhibitor dose in CHF
 NYHA class , 35% ACE inhibitor
 . 41
 16% ,
 26% . ACE inhibitor
 V - HeFT - II trial enalapril hy -
 dralazine and isosorbide dinitrate
 .⁹⁾ NYHA class , 15%(p<0.001)가
 45% 804 가 , 25%가
 1 enalapril 34% , 2
 28%가 ACE in - ACE inhibitor 가
 hibitor neuro -
 hormonal inhibitor
 . 32 meta - an - Angiotensin II receptor blocker
 alysis ACE inhibitor 가 Fig. 2 angiotensin II가
 23%, 가 35% kininase ACE nonACE system
 .¹⁰⁾ ACE inhibitor non ACE system
 가 angiotensin II
 ACE non ACE system
 ACE inhibitors in asymptomatic left ventricular sys - ACE 가
 tolic dysfunction 가 non ACE system
 SOLVD treatment trial SOLVD prev - ang -
 ention trial .¹¹⁾ Prevention trial iotensin receptor blocker
 35% . Angiotensin II receptor subtype 1 2
 . 4,228 Table 3 . subtype 1
 26%가 digoxin , receptor angiotensin II
 33%가 NYHA class subtype 2 receptor 가
 prevention trial 8% .⁴⁾

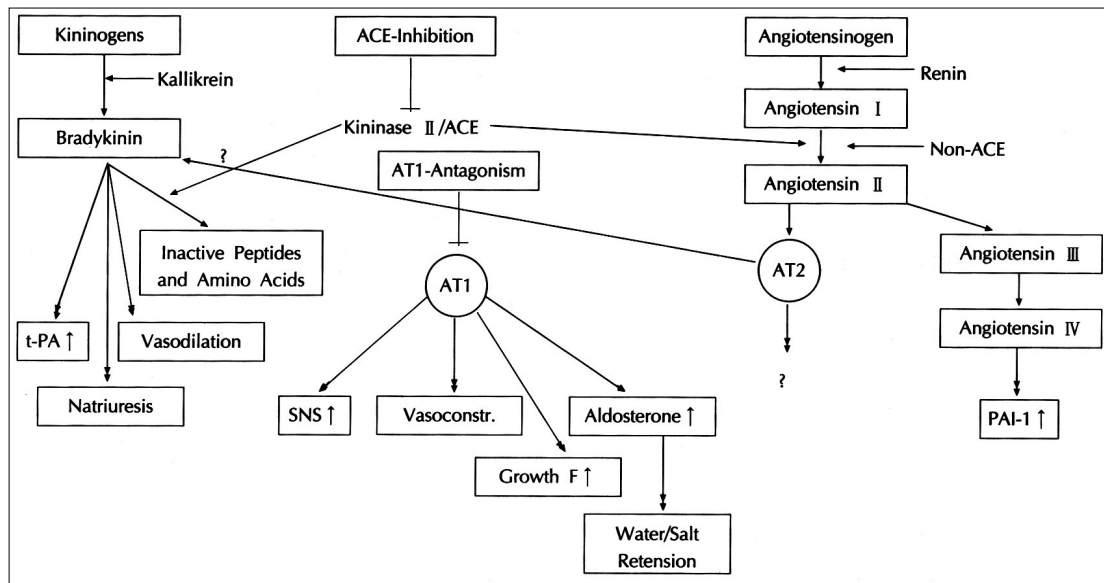


Fig. 2. Cascades of RAS and mechanism of action of ACE inhibitors and AT1 receptor antagonists. AT = Angiotensin receptors ; t-PA = tissue plasminogen activator ; SNS = sympathetic nervous system ; Growth F = growth factors ; PAI = plasminogen activator inhibitor.

Table 3. Angiotensin receptor subtype : effect

Angiotensin	R subtype	Angiotensin	R subtype
Fibrosis		Nitric oxide release	
Vasoconstriction		Antiproliferative effect	
Matrix growth		Apoptosis	
PA-I synthesis			
Endothelial dysfunction			

가 Angiotensin receptor subtype blocker가
 ,
 가 . Subtype blocker losar -
 tan ACE inhibitor captopril EL -
 ITE study ¹³⁾ losartan captopril
 , sudden cardiac
 death가 . ELITE study primary endpoint가
 primary endpoint
 ELITE study가 losar -
 tan captopril
 가 .

Angiotensin receptor blocker (ACE inhib -
 itor)

1) Greater accessibility to tissue renin - angioten -

sin system

- 2) Relative lack of aldosterone escape
- 3) Smoother hypotensive effect
- 4) Reduction of sudden cardiac death
- 5) Lesser drug interaction with NSAIDS
- 6) Uricosuric effect
- 7) Favorable effect on diastolic dysfunction

Combination with ACE inhibitor

Fig. 2 angiotensin blocking
 angiotensin 가 가 an -
 giotensin , 가 plasminogen ac -
 tivator inhibitor - 1 가 artherogenic,
 thrombogenic effect가 가 , ACE inhibitor
 bradykinin 가가 bradykinin
 t - PA 가, vasodilation, natriuresis 가
 . ACE inhibitor
 angiotensin 가가 , brady - kinin
 가가 .

가
 hemodynamics

¹⁴⁾

가

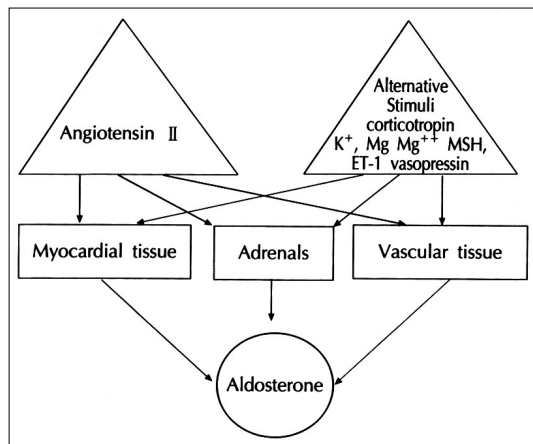
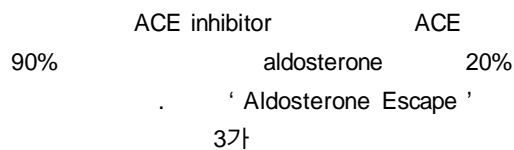


Fig. 3. Stimuli generating aldosterone.

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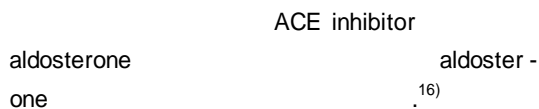
Aldosterone antagonist

Aldosterone escape and harmful effects of aldosterone



15)

- 1) Inactivation of aldosterone due to decreased hepatic blood flow
- 2) Escape of angiotensin during ACE inhibitor therapy
- 3) Generation of aldosterone from others than angiotensin (Fig. 3)



- 1) Magnesium depletion by increasing urinary output
- 2) Sympathetic activation
- 3) Parasympathetic baroreflex inhibition
- 4) Induction of ischemia due to sympathetic activation, coronary vasoconstriction by magnesium depletion and progression of atherosclerosis

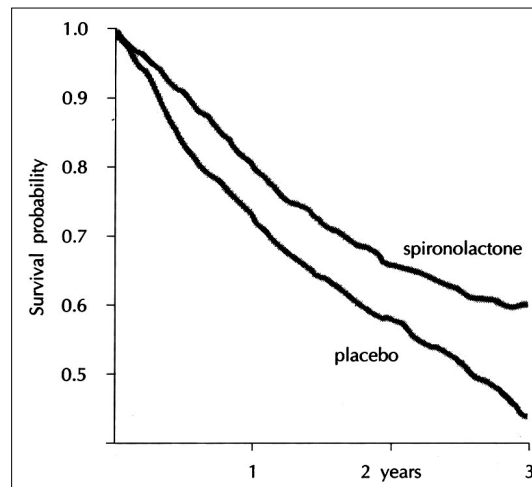


Fig. 4. The results of RALES.

- ### 5) Myocardial fibrosis

- 6) Induction of ventricular arrhythmias by magnesium depletion, sympathetic activation, parasympathetic inhibition, myocardial fibrosis, and myocardial ischemia

aldosterone 가
sudden cardiac death

Aldosterone antagonist

agonist spironolactone ACE inhibitor aldosterone antagonist . Spironolactone

가 ' RA -

LES' 17)

1,663

ACE inhibitor	spironolactone	placebo
0.0001)	Spironolactone	26%(p< 29.5%

(Fig. 4). sudden cardiac death가 20%

. Spironolactone 가

gynecomastia 9%

가

	aldosterone antagonist	spironolactone
olactone		spironolactone
lactone	gynecomastia	

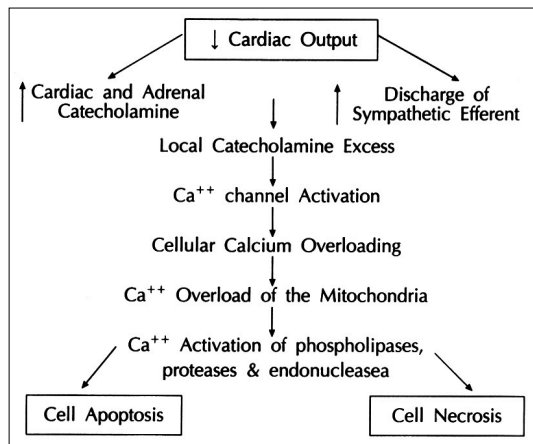


Fig. 5. Harmful effect of prolonged sympathetic stimulation on cardiac myocytes.

Sympathetic System

Harmful effect of prolonged sympathetic stimulation in heart failure

- sympathetic system
- 1) cAMP ↑, calcium ion ↑, cell necrosis (Fig. 5).
 - 2) terminally differentiated cell growth, oxidative stress, apoptosis (Fig. 5).
 - 3) Vasoconstriction, hypertrophy, myocardial ischemia.
 - 4) myocardial hypertrophy and fibrosis increase cAMP and automaticity by acting on β_2 -adrenoreceptor, hypokalemia by acting on β_2 -adrenoreceptor, increase triggered automaticity by acting on β_1 -adrenoreceptor especially in myocardial ischemia.
 - 5) contractility ↓, myocardial

ischemia

sympathetic system

, in vitro

cAMP ↑

adrenergic agonist, adrenergic partial agonist(xamoterol), phosphodiesterase inhibitor(milrinone), flequinone, vesnarinone

가

가

sympathetic system

adrenoreceptor downregulation, receptor density ↓, adenoreceptor kinase(ARK)

receptor G-protein coupling

sympathetic system

Effects of β -blockers in heart failure

sympathetic stimulation

- β -blocker
- 1) energy demand ↓
 - 2) neuroendocrine system ↓, sympathetic system ↓, RAAS(renin-angiotensin aldosterone system) ↓
 - 3) high energy phosphate ↑
 - 4) pathologic remodeling(가, myocyte stretch 가)
 - 5) Microcirculation ↑
 - 6) 가
 - 7) SERCA(sarcoplasmic reticulum calcium ATPase)
 - 8) adrenergic receptor signal transduction ↓

가 - blocker Carvedilol vitamin E 10
가 carvedilol
hydroxyl adrenergic blocking
vitamin

Clinical use of β -blocker in heart failure

History of clinical use of - blocker in heart failure
- blocker 1970
- blocker
1973 Waagstein Carvedilol
59 2가 가 US
- blocker single bolus injection
- blocker
1975 7
- blocker
25)
- blocker
- blocker
Waagstein 1993 MDC(meto -
prolol in dilated cardiomyopathy) trial 26)
metoprolol placebo
total mortality need
for transplantation 가
MERIT - HF study 27)
NYHA class - , 40% 3,991
metoprolol(metoprol -
olCR/XL) 200 mg ,
total mortality가 34%(7.2% VS 11.0%
p = 0.00009), sudden death가 41%(3.9% vs 6.7%,
p = 0.002), 가 42%(p = 0.0023)
carvedilol 1 - adrenergic bl -
ocking
가 Carv -
edilol nonselective - adrenergic blocker
1 - adrenergic blocker . Adrenergic rece -
ptor level 1 : 1 = 3 : 1
carvedilol 3 - blocker vasodilating -
blocker . 3 vasodilating - blocker
bucindolol bucindolol 1 - blocker가
direct action vasodilating property가

Carvedilol
E 1000
carvedilol angiotensin endothelin
carvedilol
- blocker
Carvedilol
2가 가 US
carvedilol heart failure study . 1996 Packer
New England Journal of Medicine
28) randomized, double blind, placebo - controlled,
multicenter study . 35% ,
3 1197 ca -
rvedilol open - label phase 94.4% 1,094
6 car -
vedilol placebo total mortality가
65% (3.2% vs 7.8%, p<0.001),
82%(0.7% vs 3.3%, p<0.001), sudden death가 55%
(1.7% vs 3.8%, p<0.001), 가 27%(14.1%
vs 19.6%, p=0.036), 38%(15.8% vs
24.6%, p<0.001)
study Bristow 1996 Circulation
Multicenter Oral Carvedilol Heart failure
Assessment(MOCHA) 29) randomized,
double - blind, placebo - controlled, dose response
study 35% 3
345 6
carvedilol 6.25 mg po
bid, 12.5 mg po bid, 25 mg po bid placebo
4
6.25 mg po bid (61%), 25 mg
po bid 가 90%
carvedilol 73% 가
carvedilol 가
placebo
가
1 - selective
- blocker metoprolol bisoprolol MERIT -

HF study CIBIS - trial³⁰⁾
 (30%) 가 carvedilol
 가
 NYHA
 class - carvedilol
 metoprolol COMET 가
 가
 Meta - analysis
 - blocker
 - blocker
 total mortality (Fig. 6),
 (Fig. 7), combined endpo -
 int (Fig. 8).³¹⁾³²⁾

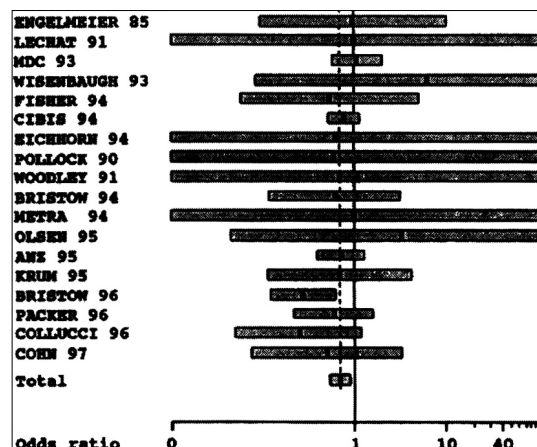


Fig. 6. -Blocker Effects on Mortality in CHF.

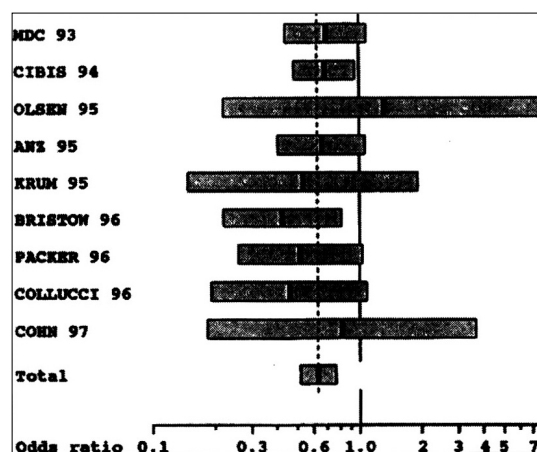


Fig. 7. -blocker Effects on Hospitalization in CHF.

Endothelin System

Endothelin
 (Fig.
 9).³³⁾ endothelin endot -
 helin receptor G protein, phospholipase
 C, protein kinase C, cell prolife -
 ration . Endothelin 3 subtype
 (endothelin 1, -2, -3) endothelin - 1
 . Endothelin receptor type A B가
 . Type A receptor
 cell proliferation ,
 type B receptor inhi -

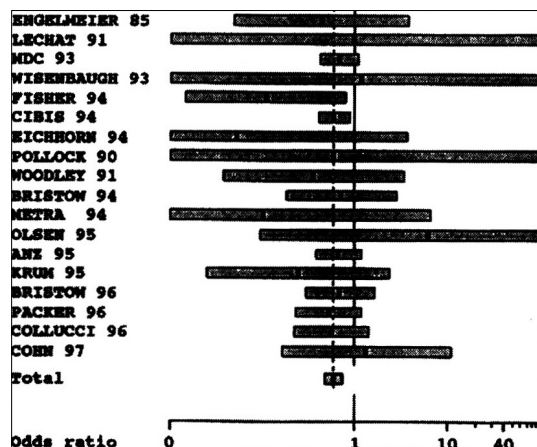


Fig. 8. -blocker Effects on Combination in CHF.

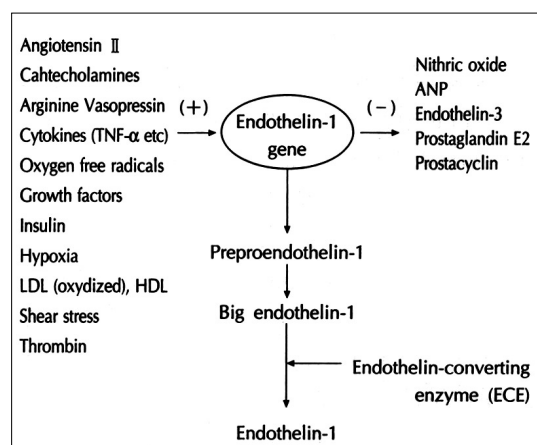
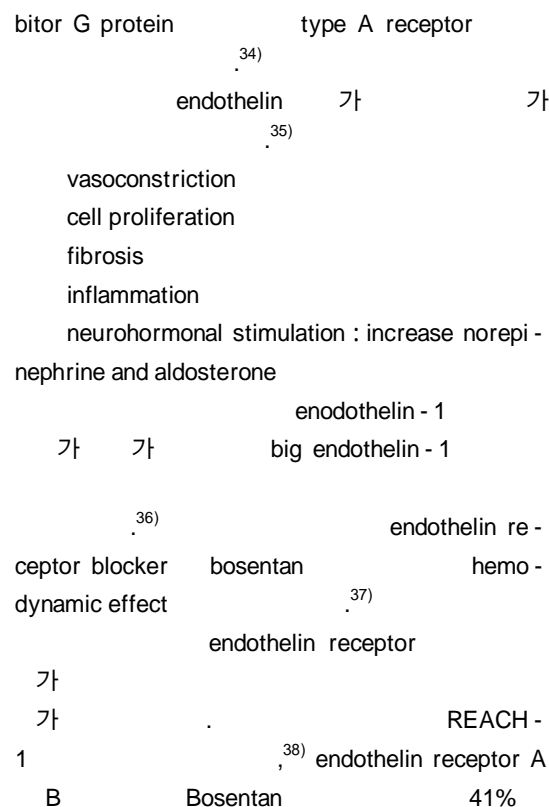


Fig. 9. Generation of endothelin-1.



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