Internal Medicine Grand Rounds

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The ABCs of ACE, CAD and CHF

or

The Diverse Effects of Angiotensin Converting Enzyme Inhibitors on the Progression of Coronary Artery Disease and Congestive Heart Failure

Craig Malloy, M.D.

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Dr. Malloy is a professor in the Departments of Radiology and Internal Medicine. His clinical interests are in CCU medicine, and his research focuses on development and application of stable isotope methods for analysis of metabolism in the heart and liver.

REDUCING MORTALITY AFTER MI: THE ROLE OF ACE INHIBITORS

Immediate therapy for myocardial infarction includes restoration and maintenance of patency of the infarct-related artery, controlling unusual hemodynamic loads on the left ventricle, and relieving discomfort. Among these high-priority items for many patients should be initiation of an ACEI, although the requirements in terms of precise dose and timing of initiation to achieve the full benefit remain somewhat uncertain. Over the last decade several trials have been reported which generally described a favorable effect of ACEI for patients with either LV dysfunction or with MI (and both in 3 instances). However, the mortality rates in the control populations varied by a factor of 6. Furthermore, the magnitude of benefit varied from about 5 patients saved per 1000 treated to 180 patients saved per 1000 treated. Obviously, dramatically different patients were studied in these trials and the benefit you should anticipate from ACEI will be highly patient dependent (see Table 2). In this section, the major trials are reviewed briefly with an emphasis on their distinctive features. The timing of drug administration in the 7 post-MI trials are shown in Figure 1, and an overall classification of all 11 trials reviewed here is shown in Figure 2.

Table 2. Summary of ACEI trials. "Initiation" refers to the average time to beginning ACEI therapy after MI. Abbreviations: p MI, post myocardial infarction; LVD, left ventricular dysfunction; ns, not significantly different.

						mortality		
study	type	patients (n)	drug	initiation (days)	follow up (months)	control (%)	ACEI (%)	
SAVE	p MI	2,231	captopril	11	42	25	20	*
CONSENSUS 2	p MI	6,090	enalapril	< 1	6	10.2	11.0	ns
AIRE	p MI	2,006	ramipril	5	15	23	17	*
ISIS-4	p MI	54,824	captopril	< 1	1.2	7.33	6.87	*
GISSI-3	p MI	18,985	lisinopril	< 1	1.5	7.1	6.3	*
SMILE	p MI	1,556	zofenopril	< 1	1.5	6.5	4.9	**
TRACE	p MI	1,749	trandolapril	4	48	42.3	34.7	*
CONSENSUS 1	LVD	253	enalapril	> 60	6	44	26	*
V-HeFT 2	LVD	804	enalapril	> 90	24	25	18	***
SOLVD TREAT	LVD	2569	enalapril	> 30	41	39.7	35.2	*
SOLVD PREVENT	LVD	4228	enalapril	> 30	37	15.8	14.8	ns

* $p < 0.05$, ACEI vs. placebo
** $p = 0.19$
*** $p = 0.08$, ACEI vs. combination hydralazine and isosorbide dinitrate

Day of admission - captopril, lisinopril, enalapril, or zofenopril?

The single largest trial of ACEI after MI is ISIS-4 which examined the effects of oral captopril in more than 58,000 patients with suspected or definite MI. ECG changes were not required. Captopril was given orally to clinically stable patients within 24 hours of the index infarction at a dose of 6.25 mg, po. Later, the dose was titrated to 50 mg po bid. Mortality at 5 weeks was 7.33% in the placebo group and 6.87% in the control group. Captopril did not interact with the other interventions (nitrates and magnesium) examined in this trial. Thus, captopril can be given early and safely with a modest mortality benefit to patients without hemodynamic instability, ongoing ischemia or contraindications to ACEI.

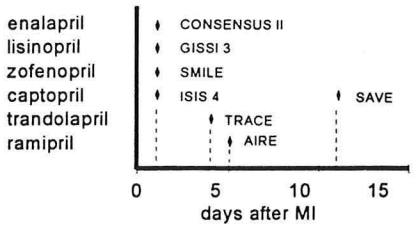

Figure 1. Seven trials, six drugs. The mean time to ACEI initiation is shown.

The second largest trial of ACEI after MI was the GISSI-3. Lisinopril was studied in about 19,000 patients, and, like ISIS 4, it was an indiscriminate trial. In other words, essentially all patients were treated, with the exception of those with specific contraindications to ACEI, valve disease, ongoing ischemia or hemodynamic instability. Like ISIS 4, a modest but highly statistically significant mortality benefit was observed (Table 2).

The effects of the early rapid delivery of an ACEI was tested by Nordic cardiologists and physicians in CONSENSUS 2. The background of this study was CONSENSUS (or CONSENSUS 1) which described a decade ago the most dramatic mortality benefit ever reported for therapy of heart failure. The first CONSENSUS trial which enrolled patients with severe congestive heart failure was terminated prematurely because of the profound mortality benefit of enalapril. The CONSENSUS 2, published 5 years later, randomized 6090 patients to i.v. enalapril within 24 hours after MI. There were no restrictions on the presence of heart failure or requirement for left ventricular dysfunction. Like its predecessor, CONSENSUS 2 was terminated early, but this time for the "statistical futility" of proceeding, since there was an insignificant trend suggesting increased mortality among patients treated with enalapril. This is an extremely important study because the average time to i.v. ACEI was rapid, about 15 hours after chest pain which included time to give thrombolytic therapy. This study indicates that immediate indiscriminate ACEI is not required.

Zofenopril was studied in the SMILE trial which selected a population, patients with anterior MI, who might be expected to have a higher mortality rate in the control groups than the other day one trials. Unexpectedly, the opposite was true: the lowest placebo mortality rate of all the trials in Table 2 was reported in this study. Nevertheless, a statistically significant benefit was reported for the combined endpoint of death or severe CHF. The mortality difference in the 2 groups was not significant.

Why was there a discrepancy between the CONSENSUS 2 and the other 3 "day one" trials? Probably because patients with MI are not a homogeneous group. For example, in GISSI-3, over 75% of the patients never showed evidence of CHF. As noted in Figure 2, none of the day one trials required depressed

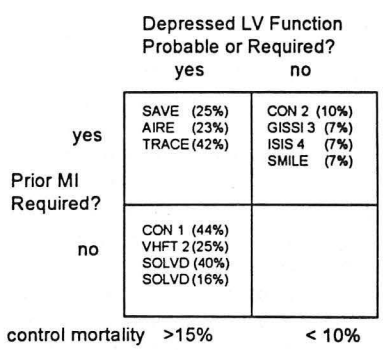

Figure 2. Classification of the 11 trials (Table 2) based on enrollment criteria. Mortality rates in the control groups are shown.

LV function, and the follow-up in these trials was generally short. Both are factors in the low mortality in the placebo groups. These observations can be contrasted with trials involving later therapy in higher-risk patients. Finally, results from CONSENSUS II were likely available during enrollment in GISSI 3 and ISIS 4 which may have swayed physicians from enrolling borderline (i.e., sicker) patients if no benefit was expected.

The ISIS investigators provided a summary of the randomized trials which were available up to that point which included GISSI, CONSENSUS II and a dozen others. More than 100,000 patients were randomized in this combined analysis, and the overall results supported ISIS-4: early ACEI therapy reduces mortality with a high statistical significance ($p < 0.001$) and a modest numerical benefit (5 deaths averted per 1000 patients treated).

Day 3 to 16 - Captopril, ramipril or trandolapril for patients with MI and LV dysfunction

The SAVE trial tested the hypothesis that captopril would attenuate morbidity and mortality after myocardial infarction. Recurrent myocardial infarction was identified prospectively as a secondary endpoint. Patients with an ejection fraction < 40% were randomized to captopril or placebo between 3 and 16 days after MI. Patients were followed for 42 months with the target of 50 mg po tid. Death and progressive heart failure were reduced in frequency in the active treatment group, and, interestingly, the risk of recurrent infarction was reduced by 25% (see Table 3 for results from other trials). The discrepancy between the results with enalapril (CONSENSUS 2) and captopril (SAVE) may be due to an adverse effect of enalapril on remodeling (defined below) or other factors. Most likely, however, is the trial design. In SAVE, reasonably high-risk but stable patients were selected for asymptomatic LV dysfunction and were followed for 42 months. CONSENSUS 2 accepted all patients which included many low-risk patients who are not likely to benefit. It also included rapid administration of the drug in a population including patients who may have had borderline hemodynamic stability.

AIRE was a study of ramipril with an interesting design twist. This study is unique among those reviewed here since it required *both* an MI *and* clinical evidence of heart failure. This evidence could be transient or sustained, but patients were excluded if they had severe congestive heart failure. Some of the other studies certainly enrolled patients with clinical failure, but this is the only one that required it. (Hence the study's location in Figure 2.) The initial dose was ramipril 2.5 mg po bid, and the target was 5 mg po bid. With an average of 15 months follow up, mortality was significantly decreased (from 23% in control to 17% in patients randomized to treatment).

TRACE also presented an interesting feature: depressed LVEF (< 35%) was documented in all patients prior to randomization on day 3-7 after the MI. The follow up of the 1749 randomized patients was carried out over 24-50 months. Of the 7 post-MI studies, TRACE selected overwhelmingly the highest risk patients (control mortality of 42%), and a highly significant mortality benefit ($P<0.001$) was demonstrated.

Day > 30: The impact of enalapril on mortality in chronic LV dysfunction (usually due to CAD)

The Studies of Left Ventricular Dysfunction (SOLVD) were designed to test the effects of enalapril in patients with symptomatic heart failure (NHYA II or III, 2569 patients, treatment study), or essentially without symptomatic failure (largely NYHA class I, 4228 patients, prevention study). The treatment trial found a significant mortality benefit of enalapril, but the prevention trial did not. However, an improved outcome was observed in the prevention trial using the combined endpoints of death and admission to the hospital for heart failure. These results are reasonably consistent with the CONSENSUS which examined much sicker patients and indicate that symptomatic CHF identifies a high risk population which will benefit from ACEI. This is important since the ejection fractions in the prevention trial (LVEF, 28%) were not substantially better than in the treatment trial (25%).

Table 3. Effect of ACEI on subsequent myocardial infarction. Abbreviations: p MI, post myocardial infarction; LVD, left ventricular dysfunction; ns, not significantly different.

study	type	drug	follow up (months)	reduction in risk of late MI
SAVE	p MI	captopril	42	25%
CONSENSUS II	p MI	enalapril	6	0% (ns)
AIRE	p MI	ramipril	15	10% (ns)
SMILE	p MI	zofenopril	1.5	37% (ns)
TRACE	p MI	trandolapril	48	13% (ns)
SOLVD TREATMENT	LVD	enalapril	41	28%
SOLVD PREVENTION	LVD	enalapril	37	14% (ns)

The unexpected finding in SOLVD was the reduction in the frequency of myocardial infarction and admission for unstable angina (Figure 3). In the prevention trial, enalapril educed the relative risk of unstable angina by 14%. In the treatment arm of the same trial, the relative risk of USA was reduced by 27%. Other studies (Table 3) have examined the frequency of myocardial infarction after enrollment in these trials. Results are somewhat inconsistent in that not every study shows a significant decline in the risk of MI among patients randomized to ACEI. However, the trend in every study (except CONSENSUS II, as expected) was similar.

Why do ACE inhibitors reduce mortality and MI among patients with CHF or with recent MI?

Based on examination of a single trial, it is not obvious which of many factors - coronary artery disease, prior MI or LV dysfunction - identifies the patients who will benefit the most from ACEI. As a generality, the use of ACEI among patients can be divided into two categories: selective trials which enrolled patients with obvious or at least evident LV dysfunction (CONSENSUS I, SAVE, TRACE, SOLVD, AIRE), and trials which enrolled virtually every patient regardless of LV function (ISIS-4, GISSI-3, CONSENSUS II, SMILE). As a further generality, the most dramatic mortality benefits of ACEIs are confined to patients treated in the selective trials. Therefore, some degree of LV dysfunction rather than simply prior MI identifies patients who will benefit.

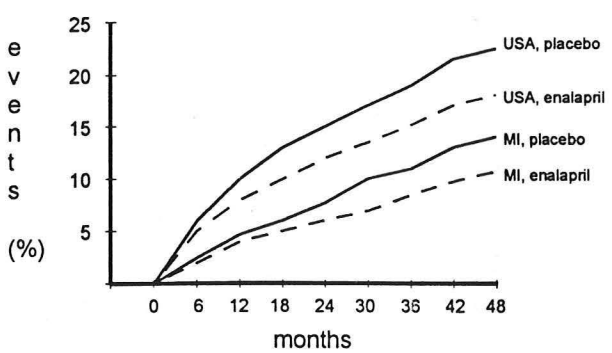

Figure 3. Risk of ischemic events among patients with LVEF < 35% (redrawn from Yusuf, *et al.*, Lancet 340: 1173, 1992). USA, unstable angina. Results were from the two SOLVD trials, treatment and prevention.

The mechanism(s) of reduced MI and reduced mortality rate observed in these patients are unknown, but could be due to at least 3 factors: a beneficial effect on the coronary artery disease, a beneficial effect on the systemic impact on progression of

heart failure unrelated to the cause of LV dysfunction, or an effect on the uninvolved myocardium and perfusion in that tissue.

SOLVD found that asymptomatic patients with LV dysfunction remote from MI treated with ACEI (enalapril) had no mortality benefit, and no adverse effects. These observations suggest that the benefit of an ACEI after acute MI are not due to retarding the overall systemic response to LV dysfunction since benefit was not observed in SOLVD prevention where the average EF was 28%. Furthermore, enalapril was superior to the combination of hydralazine and isosorbide dinitrate in V-HeFT 2 which suggests that simple arteriolar and venous dilation does not achieve the full benefit of ACEI. It is unlikely that the hypotensive effects of ACEI alone are responsible, since hydralazine does not modify LV dilation even when mean arterial pressure is identical to captopril therapy in animal studies. A decrease in preload (which occurs with captopril but not hydralazine) has been considered, but aggressive furosemide therapy does not modify remodeling, at least in patients.

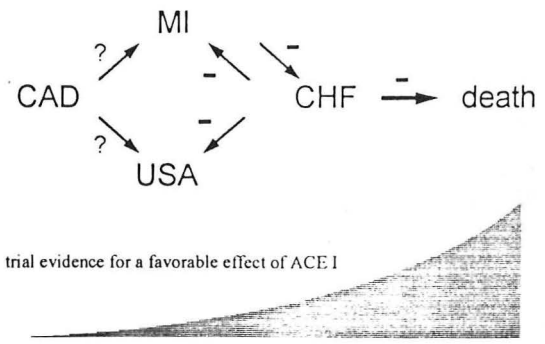

Figure 4. How solid are the results from clinical trials?

Conclusions from the randomized trials

As a group, most patients do well after MI. Therefore, adding a drug should have clear benefits with minimal risk. Overall, the ACEIs fit that target for a wide range of patients, but several points should be taken from these clinical trials.

First, the indiscriminate day one trials in fact imposed some restrictions. Although "all patients" were to be enrolled, various exclusion criteria were used which were reasonable and typically included hypotension, severe CHF, onging ischemia, valvular heart disease and contraindications to these agents.

Second, CONSENSUS II is the only day one trial to use an iv agent within hours after the MI. The initial captopril dose in ISIS 4 was low, and, although captopril is quickly absorbed, the ACEI inhibition was likely brief. Lisinopril used in GISSI 3 is absorbed slowly (5-8 hours). It is plausible (but speculation) that CONSENSUS II was the earliest effective administration of sustained ACEI therapy. Its outcome may indicate that very early sustained ACE inhibition may be harmful if administered indiscriminately.

Third, the magnitude of mortality benefit in the day one trials is unequivocal, but modest.

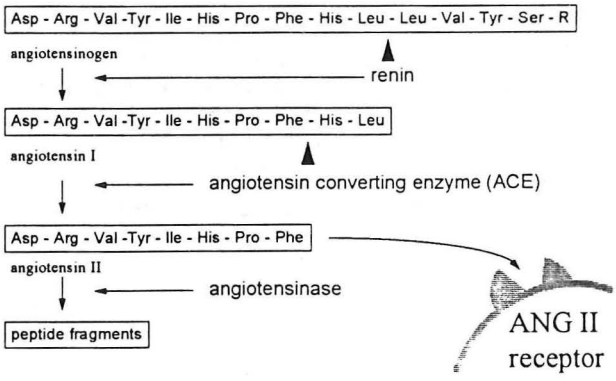

Figure 5. Metabolism of angiotensinogen.

Fourth, high risk patients - those with an MI and either clinical CHF or depressed ejection fraction, or both, will benefit dramatically from ACEI. It is not necessary to begin ACEI therapy in the first day to achieve this benefit - the relevant trials randomized patients at an average of 4, 5 or 11 days to therapy.

Fifth, progression of CHF with recurrent MI and unstable angina may be retarded by chronic ACEI inhibition, but this has been strongly suggested in only 2 trials - the other relevant trials did show a trend in the same direction.

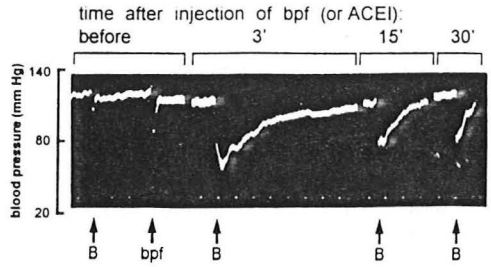

Figure 6. Arterial blood pressure in a cat. B, iv injection of bradykinin; bpf, injection of bradykinin potentiating factor. See text for details. Redrawn from Br. J. Pharmacol. 24: 163-169, 1965.

In sum, the magnitude and the reliability of mortality reduction due to ACE inhibition is summarized in Figure 4.

ANGIOTENSINOGEN, KININOGENS AND CONVERTING ENZYME INHIBITORS

One of the fascinating stories of modern pharmacology was initiated 100 years ago when Tigerstedt and Bergman described the enzyme renin. Over the last century a rather complete description of the renin-angiotensin-aldosterone endocrine system (RAAS) has been elucidated, and the relations among renin, angiotensin I and angiotensin II are summarized in Figure 5. From the traditional endocrine perspective, ANG II is a hormone which has profound systemic actions. More recently, tissue-specific expression of renin, angiotensinogen, angiotensin converting enzyme and angiotensin II receptors have all been demonstrated in the heart. Thus, the renin-angiotensin system is not only an endocrine system, but a paracrine system, as well.

The development of ACEIs was initiated about 30 years ago. By the early 1960s, the basic relations among ANG I, ANG II, ACE and renin (Figure 5) were known. Until the mid 1960s, the only known inhibitors of ACE were nonspecific divalent metal ion chelators which removed zinc from the enzyme. In 1965, Ferreira (18) showed that a relatively nontoxic ethanol extract from the venom of *Bothrops jararaca*, a pit viper native to the Brazilian forests, potentiated all of the effects of bradykinin (Figure 6). Later, Ferreira showed that this extract contained 9 small peptides. Because of the similarity in amino acid sequence between ANG I and bradykinin, the effects of this extract, bradykinin potentiating factor, on ACE were tested, and significant inhibition was demonstrated. Subsequently, these peptides were sequenced and numerous synthetic peptides, among them teprotide, were developed. Although these compounds had significant ACE inhibition and antihypertensive effects, they could not be given orally. The potential for an orally active ACE inhibitor was appreciated, and captopril was developed in one of the first examples of rational drug design based on knowledge of the enzyme structure (19).

An important feature of ACEIs is implicit in their history. ACE is identical (Figure 7) to kininase II which degrades bradykinin. Therefore, inhibition of ACE also inhibits the degradation of bradykinin which may play a role in the cough associated with ACEI (see below), but more importantly bradykinin or related vasodilators may play a direct role in the beneficial effects of ACEI.

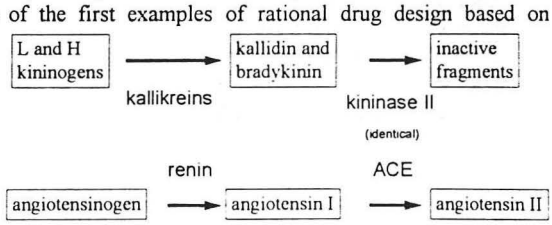

Figure 7. Kininase II and angiotensin converting enzyme.

Tissue specific expression of the RAS is suspected to be critical in the long-term effects of ACEI as well as the steady deterioration observed in some patinets with CHF. However, it is not clear which system (systemic RAAS or cardiac RAS) is dominant. For example, following a myocardial infarction complicated by heart failure, plasma AII levels increase and then return to normal levels. In chronic LV dysfunction the circulating renin-angiotensin system is activated to a variable degree. In animal models there is early increased expression of angiotensinogen and ACE in the residual normal myocardium after myocardial infarction. In the setting of acute volume loading there is a rapid increase in renin expression in the left ventricle. Although the cardiac renin-angiotensin system is clearly activated after MI in acute animal models, the mechanism of this activation is uncertain. Most importantly, the relevance of these observations in human CHF is unknown.

To address this critical question, one approach is to activate the cardiac renin-angiotensin system and to examine the consequences for cardiac function. When the tissue renin-angiotensin system is activated (in renin transgenic rats), the circulating RAAS is not activated. In comparison to spontaneously hypertensive rats (which are low renin models of hypertension), the transgenic rats showed extensive fibrosis and scarring which correlated with depressed left ventricular function compared to the spontaneously hypertensive rats. Studies of this type illustrate that the extent of end organ damage may be quite different even if the level of hypertension is identical in two models. Therefore, not all end-organ damage - in this case fibrosis - is due to hypertension and evolution of hypertrophy.

REMODELING AND THE STRUCTURAL RESPONSE TO MI

Late mortality after myocardial infarction correlates with indices of left ventricular function. Diastolic dysfunction could be defined for clinical purposes as a condition in which the routine measurement of systolic function, ejection fraction, is greater than 45%, yet the patient presents with symptoms and findings which might otherwise suggest more severe left ventricular dysfunction. With this definition, heart failure due to diastolic dysfunction has about half the mortality rate of patients with systolic dysfunction (20). Unfortunately, there is no accepted index of diastolic function which is independent of the measuring technology, and little natural history information is available. Diastolic dysfunction may be relevant to the consequences of ACEI therapy, but will not be further considered.

Systolic dysfunction and its relation to prognosis after MI, on the other hand, has been studied exhaustively. Hemodynamic parameters have been reported in small trials of highly selected patients. Since invasive monitoring is required, natural history information is not widely available, and the individual predictive power of each possible measurement is unknown. High left ventricular end diastolic pressure, high right atrial pressure, high pulmonary capillary wedge pressure, low stroke work index and low cardiac index all correlate with poor survival. As a general rule, the original conclusions by Forrester and colleagues 25 years ago still apply: elevated pulmonary capillary wedge pressures and reduced cardiac output predict poor outcome.

The ejection fraction can be measured by numerous methods (both invasive and noninvasive) and it is perhaps the most widely used index of overall LV function. This parameter has been extensively studied in prospective reports which correlate EF with survival. End systolic and end diastolic volumes also correlate with mortality after MI, and, like the hemodynamic indices, it is difficult to determine the independent predictive value of each with respect to mortality. In the thrombolytic era, it appears that end systolic volumes or the end systolic volume index is at least equivalent and perhaps better than the other measures in predicting mortality.

Why does the ventricle dilate after myocardial infarction? Myocardial infarction produces changes in left ventricular geometry of 2 types. Early after infarction these changes are predominantly in the necrotic region and consist of thinning, loss of wall motion and ultimately scar formation. Later, the anatomical alterations are more prominent in the noninfarcted region and are characterized by hypertrophy. The extent of these regional

changes in myocardial mass and global changes in left ventricular shape and volume have been proposed to mediate the beneficial effects of ACEI, and for this reason will be considered in more detail.

What is remodeling?

The term "remodeling" is widely used in the ACEI literature. From a hemodynamic perspective, ventricular remodeling refers to a change in the shape or volume of the left ventricle which cannot be attributed to short term or acute events such as drug administration, changes in hemodynamic loading conditions, or recent or ongoing ischemia. It is important to appreciate that global measurements of left ventricular function (ejection fraction, end systolic volume, end diastolic pressure, etc.) reflect a very complex interplay of healing, dilation and hypertrophy among normal tissue and infarcted tissue, so remodeling in the usual clinical context refers simply to global left ventricular parameters (length to radius ratio, EF, end systolic volume, etc.). In this sense remodeling can indeed be followed by clinical tools, but it is important to recognize their limitations. Remodeling also indicates reorganization of the left ventricle and coronary arteries at a cellular and subcellular level which are not be directly evident by clinical measurements. For example, investigators refer to myocyte, matrix and endothelial remodeling in the context of the effects of ACEI.

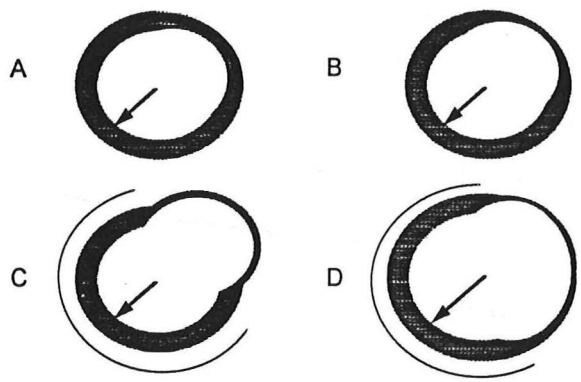

Figure 8. Schematic effects of infarction and infarct expansion on LV radius. Frame A shows a short axis section of a normal ventricle at the time of MI (black arc). If the infarction heals as an akinetic segment without expansion, the short axis radius may change little (B). However, with infarct expansion (C) and overall dilation of the LV (D), the short axis radius and therefore wall stress must increase even if ventricular loading conditions are normal.

Remodeling in the infarct segment: Infarct expansion and early enlargement

Infarct expansion refers to thinning of the infarct region which is not due to further infarction and necrosis. This progressive dilation and thinning has the effect of increasing the fraction of left ventricle which cannot contract, and the occurrence of dilation correlates with poor prognosis. Prior to routine aggressive reperfusion therapy, this phenomenon was thought to occur in 70% (21) of Q wave infarcts which are more likely to be transmural. On the other hand, expansion is rare in non Q wave infarcts (22, 23). Even in the era of primary angioplasty and thrombolysis, the left ventricle may dilate rapidly in the first few days after infarction, and the dilation results predominantly from tissue lengthening in the region of infarction (24). This process is most common with anterior infarctions and with unrelieved afterload early during the infarct. This thinning is due to both myocyte dropout and necrosis, and myocyte slippage.

Remodeling of the noninfarcted region - late enlargement and a stimulus for hypertrophy

Early dilation of the left ventricle is usually due to infarct expansion, but later enlargment of the left ventricular cavity is due to lengthening of segments in the noninfarcted region. This lengthening is essential to maintain normal nor near -normal stroke volume because normal myocardium can shorten to a limited degree in spite of maximal inotropic stimulation. As illustrated in Figure 8, rearrangement of the left ventricle due to

infarct expansion (or segment lengthening) inevitably has its cost: wall stress in the normal myocardium is increased. Thus, even if intraventricular pressures are normal, the stimulus to hypertrophy, increased wall stress, is present.

This chronic increase in average wall stress in the noninfarcted region is thought to provoke the characteristic response of the LV to increased load, ventricular hypertrophy. Generally, pressure overload hypertrophy is assumed to cause parallel addition of new myofibrils ("concentric" hypertrophy), and volume overload hypertrophy is assumed to cause series addition of myofibrils ("eccentric" hypertrophy). In addition to the obvious flaws in this terminology (why has it persisted?), it is likely that the cellular, biochemical and molecular features of the noninfarcted segment are a mixture of both volume and pressure overload hypertrophy. This mechanical stress is though to produce remodeling in the noninfarcted myocardium at a cellular level.

Myocyte remodeling: Glycolysis, mitochondrial function, energy transfer and contractile proteins

One characteristic feature of hypertrophied and failing myocardium is abnormalities of intermediary metabolism and mitochondrial function. Thirty years ago an important research question was whether mitochondrial failure was cause or consequence of hypertrophy and failure. Although the question remains unanswered, several differences between normal and hypertrophied/failing myocardium are known. Perhaps the best studied effect in intermediary metabolism is the increase in glycolysis (25). It was suggested that generation of glycolytically-derived ATP is essential to drive membrane pumps which are more active in hypertrophied myocardium. Alternatively, if hypertrophied tissue is relatively ischemic, then accelerated glycolysis is required to maintain any ATP production.

It was not clear until recently (26) that hypertrophied myocardium, even at the very early stages, preserves the capability of oxidizing carbohydrates including lactate in the citric acid cycle. This observation is inconsistent with a simple concept of hypertrophy causing ischemia. Instead, fatty acid oxidation is profoundly inhibited in animal models of LVH which may be due to impaired mitochondrial function. Since β oxidation requires intact mitochondria, this inhibition of fatty acid oxidation may be an early indicator of mitochondrial injury which is evident as reduced mitochondrial volume described below.

Morphological studies indicate abnormalities of mitochondria during the progression from normal to hypertrophied to failing myocardium. Specifically, the ratio of mitochondrial volume relative to cell volume and the ratio of mitochondrial volume to myofibrillar volume both decrease (27, 28, 29). The magnitude of these changes are substantial. For example, the fraction of myocyte volume which is occupied by mitochondria decreases from 0.42 ± 0.01 to 0.35 ± 0.01. The ratio of mitochondria seen on cross section relative to myofibrils also decreases significantly, from 0.76 ± 0.03 to 0.59 ± 0.02.

Another line of evidence indicating mitochondrial injury are recent NMR spectroscopy studies which demonstrate a decrease in phosphocreatine/ATP ratio in patients with heart failure due to valvular heart disease. Similar measurements have not been made in noninfarcted myocardium of patients after MI, but these studies do suggest that chronically increased wall stress is associated with another indicator of mitochondrial injury.

Myosin heavy chains exist in two forms, α and β, which combine as three different dimers: $\alpha\alpha$ homodimer (V_1), an $\alpha\beta$ heterodimer (V_2) or a $\beta\beta$ homodimer (V_3). Muscle which is predominantly V_3 has a lower rate of oxygen consumption per unit of force generated, and V_1 has the highest rate of oxygen consumption per unit force. In normal rats, the predominant heavy chain population is V_1, but the population shifts to V_3 with either pressure or volume overload., and the percentage of V_3 closely matches the degree of LVH. Aging, diabetes, high sodium intake and hypothyroidism all cause a similar shift to V_3. Unfortunately for an attractive hypothesis, larger mammals such as humans possess a ventricular myosin which is predominantly

V_3. Therefore, humans (and cows and pigs) do not have the same response to hypertrophy as in small mammals. The relevance of these observations in rats for human heart failure is unknown.

Remodeling in the extracellular matrix

The extracellular matrix is composed of collagen type I and III. An increase in the collagen content decreases diastolic compliance and man increase the risk of rhythm disturbance. The collagen content in normal myocardium after and MI increase in rats and humans Interestingly, DNA synthesis in the interstitium but not norm cardiomyocytes is increased for about 2 weeks.

Endothelial and arterial remodeling

In myocardial hypertrophy, the ratio of myocyte volume to capillaries is increased, that is, the hypertrophy process has outrun its blood supply. It has been proposed that this phenomenon creates relative energy starvation, although the complex interactions among perfusion, glycolysis and mitochondrial function have not been established in either hypertrophy or heart failure.

It is clear that dilation of the epicardial coronary vessels in response to some vasodilators (e.g., glyceryl trinitrate) are disrupted in patients with heart failure. At the level of resistance vessels ACE inhibitors may have important effects in heart failure. Most of the activity of endothelium derived relaxing factor is thought to be nitric oxide which is continuously released from the endothelium. Numerous abnormalities of the endothelium (atherosclerosis, hypercholesterolemia, hypertension) interfere with the stable release of NO. Since NO release is stimulated by bradykinin, it is attractive to speculate that ACEI improves the limited vasodilator response of diseased coronary arteries by enhancing the local concentration of bradykinin and simultaneously removing the vasoconstrictor effects of ANG II. Finally, in high doses in animal models, ACEI reduce smooth muscle proliferation in coronary arteries.

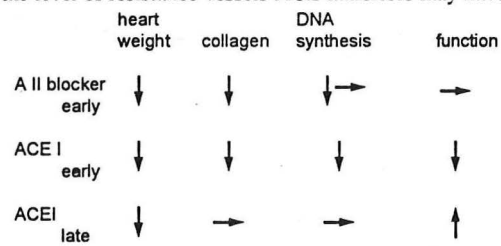

Figure 9. Influence of ACEI and A II blockers in the remodeling myocardium.

Role of ACEI in remodeling in the noninfarcted segment

The beneficial effects of ACEIs are unquestioned, but a number of important clinical issues remain unanswered. The utility of examining each component of the response to ACEIs is that it provides a framework in which to interpret the clinical trials, and perhaps provide clues about proper management.

For example, the need to use ACEIs very early in the course of MI is not clearly established, and there are theoretical concerns about early ACEI. For example, acute hypotension in a tenuous patient may cause extension of the infarct or other complications. It is therefore interesting that studies in animal models suggest a separate adverse effect: late ventricular function may be impaired. Figure 9 summarizes a series of studies (30, 31, 32) which examined in rats the effects of early ACEI (3 weeks of therapy starting at the time of MI), late ACEI (2 weeks of therapy, starting 3 weeks after MI) and early blockade of the ANG II receptor with losartan. Briefly, these studies indicate that all 3 interventions reduce heart weight. Early ACEI also reduced cardiac collagen by histochemical measures, as well as synthesis of DNA by interstitial cells. Overall, early ACEI was a general antiproliferative intervention.

However, a problem arises in cardiac function measured late after MI in these animals. Compared to controls (MI, not treated), early ACEI was associated with a lower stroke volume, higher heart rate and higher central venous pressure compared to animals not treated with ACEI. The hemodynamics of these animals indicate progression of heart failure. By contrast, the animals treated late with ACEI had a higher stroke volume, lower central pressures, and no difference in heart rate compared to nontreated animals with an infarction. These data are obviously not conclusive, but they do suggest that early ACEI may have adverse effects on healing.

ACE INHIBITORS AND CORONARY ARTERY DISEASE

Since angiotensin II is a potent coronary vasoconstrictor, it might not be surprising that interference with angiotensin II could have an immediate beneficial effect for patients with CAD and angina. However, ACE inhibition also has more complex effects on the heart, catecholamines and myocardial oxygen demand. Since inhibition of ACE decreases water and salt retention, and causes venodilation as well as peripheral vasodilation,

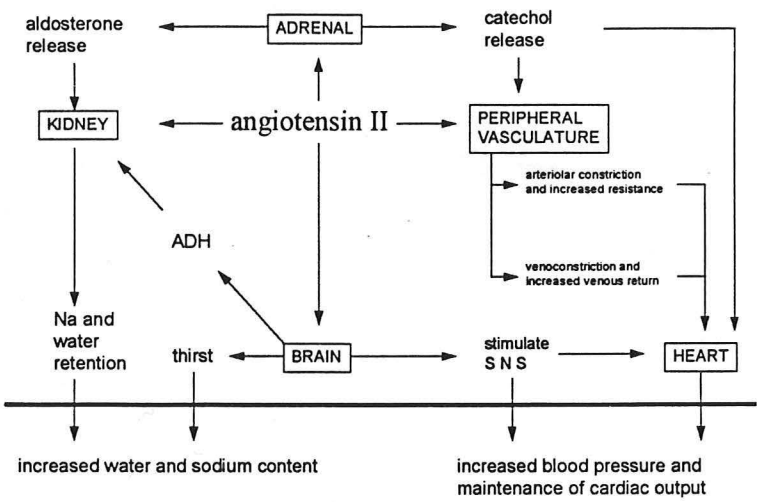

Figure 10. Effects of ACE II on the cardiovascular system.

myocardial preload and afterload are reduced. ACE inhibition also reduces direct sympathetic stimulation of the heart by reducing the activity of the sympathetic nervous system and by improving norepinephrine reuptake. Together, these effects on preload, afterload heart rate and contractility all conspire to reduce myocardial oxygen demand. Furthermore, ACE inhibition blocks not only the coronary constrictor effects of AII but also the proliferative effects of AII. ACE inhibition also inhibits the breakdown of bradykinin which directly stimulates nitric oxide release. Therefore, in theory, ACE inhibition should have both direct and indirect coronary vasodilator properties plus later antiproliferative and antithrombotic effects.

Despite this very compelling "blackboard physiology," it is not clear that ACE inhibition has a consistent immediate effect (in either direction) on myocardial ischemia which is clinically relevant. A number of small studies have examined the efficacy of ACEI in patients with stable coronary artery disease using 3 types of studies: the effects of i.v. captopril in pacing-induced angina, the effects of enalapril on exercise tolerance, and the effects of benazapril on ambulatory ST segment depression. Overall, these small studies did not

demonstrate convincing efficacy of an ACEI for these patients with angina and stable CAD, and there are small but worrisome studies demonstrating an adverse effect.

Symptoms and objective assessment of ischemia in patients with stable angina

The effects of intravenous ACEI on angina threshold and coronary lumen diameter were studied during pacing-induced angina. Intravenous captopril (33) produced coronary vasodilation at the site of atherosclerosis at rest (0.1 mm) and during ischemia (0.2 mm). In spite of this attractive effect, captopril neither improved lumen dimensions in the nondiseased vessels nor did it improve angina threshold. Somewhat conflicting results in another trial of similar design found an increase in the time to angina with pacing and a trend towards decreased coronary flow and decreased coronary vascular resistance (34).

The effects of chronic ACEI therapy in patients with chronic stable angina has yielded somewhat discouraging results. In a well-designed, double blind, placebo controlled trial, enalapril reduced systolic blood pressure at rest and with exercise (35). Since there was no effect on heart rate, the total rate pressure product was reduced. On exercise testing, enalapril prolonged the time to ST depression and it increased the exercise duration. However, the use of nitroglycerin and the frequency of angina was not improved.

Benazepril, exercise testing, and ambulatory ST segment monitoring

At least three studies have incorporated exercise testing plus ambulatory ST segment monitoring as an objective marker of ambient ischemia to assess the effects of benazepril in stable coronary artery disease. Overall, the frequency of angina, exercise duration, rate pressure product and maximal ST depression were not influenced by benazepril in 11 patients (36). It may be important to note that 6 patients improved, but 3 patients deteriorated in this protocol, so there may be considerable variability among patients. In a separate study of 29 patients (37), the exercise time and exercise induced ischemia was not improved, but there was a strong trend towards reducing total episodes of ischemia. However, neither angina frequency nor nitrate use was altered among patients using the ACEI. The largest study (38) again found no effect on exercise duration, but in 34 patients banazepril reduced reduced the magnitude of ST depression in 48 hour monitoring and altered the normal circadian variation of ischemic events.

These data show, among patients without hypertension, no beneficial or adverse effect of benazepril on angina, nitrate use or exercise tolerance. These studies hint that the severity of ischemia during ordinary activities may be attenuated.

Angina and hypertension - results are consistent with antihypertensive effects

The results are different when patients with coronary disease and hypertension (a common combination) are examined. For example, oral captopril reduces the rate pressure product in patients with hypertension and coronary disease, and as expected produces

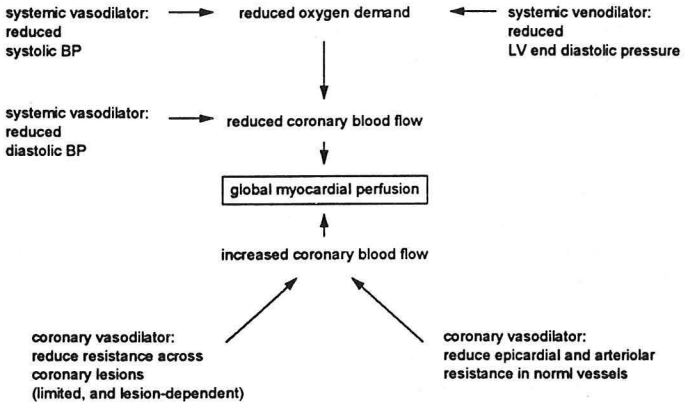

Figure 11. Influence of ACEI on myocardial perfusion.

parallel changes in myocardial oxygen consumption and coronary flow. Oral captopril also reduces blood pressure, the magnitude of ST depression with exercise, and it improved exercise duration. Similarly, perindopril dramatically improved exercise induced ischemia and reduced angina frequency.

Together, these results plus the observations with benazepril indicate that the expected antianginal effects will occur among hypertensive patients when ACEIs improve systemic blood pressure. Conversely, among normotensive patients with CAD, small studies do not suggest either improvement or deterioration in clinical status.

Coronary hemodynamics and angina in patients with heart failure

The effects of ACEI on coronary blood flow among patients with heart failure are expected to be complex because angiotensin is a potent constrictor of both coronary and systemic vasculature. The consequences of blocking this effect might be beneficial if the decrease in systemic diastolic pressure (coronary perfusion pressure) is more than counterbalanced by coronary vasodilation in both diseased epicardial vessels as well as in resistance arterioles (Figure 11). Clinical results among patients with heart failure and coronary artery disease are not as reassuring. Cleland and colleagues reported a double blind, placebo controlled crossover study which found significant adverse effects of captopril among patients with both coronary artery disease and heart failure. Captopril was associated with worsening angina, reduced exercise duration, and an increase in the number of patients who stopped exercise because of angina (39). Overall, captopril was not useful in improving angina among patients with heart failure. This study highlights the obvious problem with Figure 11: from the patient's perspective, ACEI may be detrimental because perfusion in one cornary artery may decease relative to local oxygen demand, and cause angina.

ACEI after angioplasty: MERCATOR, MARCATOR and QUIET

The prevention of angiographic restenosis was examined in two large trial of cilazapril in Europe (MERCATOR, low dose cilazapril) and in North America (MARCATOR, high dose cilazapril). Because of the antiproliferative effects of ACE and their effects on reducing the risk of recurrent MI and unstable angina, it was thought that cilazapril might attenuate restenosis, but it did not. A simpilar trial with quinapril is nearing completion. The QUIET was designed to test the effect of long-term ACE inhibition in patients with coronary artery disease undergoing PTCA, normal lipids, normal blood pressue and normal or near-normal LV function (LVEF > 40% was required). Quinapril was selected because it tightly binds the converting enzyme in both arterial and cardiac tissue. Enrollment of 1750 patients with an average ef of 59% has been completed. Patients with prior bypass surgery or recent myocardial infarction were excluded, and the study results are pending.

PRACTICAL PROBLEMS

High or low dose ACEI?

The dose you select in practice should be as close as possible to the dose used in the clinical trials which established both the therapeutic efficacy and safety of the drug. There is virtually no information about the relation between extent of inhibition of the ACE system and the beneficial effects, and there is little clinical information about the interactions between dose and timing.

A preference for low doses might be justified if low doses produce equivalent benefits to higher doses, yet high doses produce more side effects. The argument is attractive and there is some supporting evidence. Low doses of some agents (e.g., ramipril) reduce LVH even when blood pressure is unaffected (40). Another argument is that the hemodynamic effects of ACEI are not related to activity of plasma ACE. If the beneficial target is tissue ACE, then low dose agents with high tissue penetration should be perferred. Finally, if the

beneficial effects are due to inhibition of bradykinin breakdown (which may b eachieved at low doses of ACEI), then systemic hemodynamic changes may be misleading. A small clinical trial (41) found that captopril, 25 mg po bid, had an improved morbitidy-mortality endpoint.

A preference for high doses can also be justified. Regardless of the interest in bradykinin and indirect effects of ACEI, the clearest effect of ACEIs is prevention of the formation of ANG II. Low doses only inhibit the production of ANG II for a few minutes. Complete inhibition of ANG II formation requires high doses such as enalapril, at least 40 mg/day. Anything less and a small amount of enzyme is uninhibited which will lead to rapid conversion of large amounts of ANG I (which has built up) to ANG II. Furthermore, the optimal effects of ACEI on bradykinin, substance P, nitric oxide and other poorly described systems may require high doses for tissue penetration. High doses of ACE inhibitors retard progression of atherosclerosis in animals, so the "upper dose frontier" in humans should be at least explored. Finally, with careful titration, larger doses of ACE inhibitors generally produce greater hemodynamic effects with no obvious increase in toxicity.

ATLAS was performed to compare the effects of low and high doses of lisinopril on the survival of patients with heart failure. Results should be available early in 1998.

Early or late after MI?

The HEART trial was designed to compare the safety and efficacy of immediate vs delayed and low vs conventional dose ramipril in clinical stable patients immediately after an MI (42). This design is highly relevant to the modern era of aggressive reperfusion therapy. In HEART, 87% of patients received either angioplasty or lytic therapy (sometimes both), and the vast majority were treated with aspirin, heparin, ß blockers and nitrates. From the standpoint of conventional therapy for MI, these patients are representative of current practice. The HEART investigators concluded that the early use of ramipril titrated to a relatively high dose among patients with an anterior MI produced earlier recovery of LVEF. In contrast to the large trials reviewed earlier, this was not a mortality trial.

What about cough?

A dry persistent cough is induced in about 10% of patients on ACEI. It is irritatin and forces discontinuation of therapy, although in a few patients it may resolve after several days or remit after switching to a different ACEI. The mechanism of ACEI-induced cough is unknown. Since ACE is a kininase, it is involved in the breakdown of bradykinin and other mediators of inflammation. Bradykinin directly stimulated rapidly adapting stretch receptors and C fibers in the lung, although their role as afferents in te cough production is controversial (43). An alternative hypothesis is that the effects of ACEIs are mediated *via* bradykinin, but the effectors are generated by the stimulation of phospholipase A_2 which triggers the production of thromboxane A_2, a facilitator of bronchoconstriction. Recently, picotamide, a powerful inhibitor of thromboxane ynthease, was shown to abolish the cough induced by enalapril (44). Since picotamide is an antiplatelet agent, it is theoreticaly attractive to recommend routinely combining this agent with an ACEI for patients with LV dysfunction who are at risk for complications of coronary disease.

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