"Heart Failure Redux"

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This *Heartbeat* will revisit the heart failure (HF) problem and evaluate some promising new approaches. In the US today, HF management continues to be a growing medical challenge with incidence approaching 5 million and yearly mortality approaching 250 thousand. Therapeutic strategies for HF are based on the notions of restricting fluid retention and inhibiting neurohumoral systems, notably the renin-angiotensin and sympathetic systems. Guidelines recommend a combination of diuretics, ACE-inhibitors and beta-blockers with or without digoxin as a basis for treatment. Aldosterone inhibitors are recommended for more severe HF.

Emerging importance of "triage" BNP

Because patients with left ventricular (LV) systolic dysfunction (LVEF< 40%) have improved survival and improved quality of life on medications such as ACE-inhibitors and beta-blockers, it is imperative to make the correct diagnosis as accurately and as early as possible. This is especially true in the emergency room. Results from the **B**rain Naturetic Peptide for **A**cute **S**hortness of Breath **E**va**L**uation (**BASEL**), presented at the European Society of Cardiology Congress last month showed that BNP testing reduces the time to initiation of therapy, the time to discharge and total treatment cost.

B-type (brain) natriuretic peptide, or BNP, is a neurohormone released by the cardiac ventricles in response to volume expansion and pressure overload. The BNP, a bedside blood test, correlates BNP level to presence or absence of CHF in patients with acute or chronic dyspnea. The **B**reathing **N**ot **P**roperly (**BNP**) trial found that BNP testing had a diagnostic accuracy of 83.4% (using a cut-off of 100 pg/ml or higher).[1] Low levels of BNP (100pg/ml) make the diagnosis of HF unlikely. This cutoff allows for the increased concentrations observed with advancing age—more so in women (stiff ventricles). Its negative predictive value was 96% (using a cut-off of 50 pg/ml or less). A very high level "strongly argues" that the cause of dyspnea is HF. BNP testing for congestive heart failure (CHF) is as good as or better than methods used to diagnose prostate, cervical, and breast cancer, according to investigators. Right now, ***BNP is used fairly routinely in emergency departments to differentiate patients who have shortness of breath due to non-cardiac causes and patients who have heart failure. It is most helpful when the diagnosis of HF was intermediate.***

Critics are quick to point out that BNP is at its weakest in this intermediate range and clinical judgment is still the most important part of diagnosis. In a patient presenting with dyspnea, HF is *usually absent* at B-type natriuretic peptide (BNP) levels less than 100 pg/mL, *possible* between 100 and 500 pg/mL, and *probable* at levels greater than 500 pg/mL. BNP levels between 100 and 500 pg/mL may also be seen in patients with known left ventricular (LV) dysfunction, lung disease (BNP produced from the right ventricle), renal failure, myocardial infarction, or pulmonary embolism. BNP is increased in patients with end stage renal disease (pre-dialysis) and in virtually all on dialysis—probably secondary to volume overload.

Although the current rapid assay has only been approved for diagnosis, it may be of assistance in risk stratification, determining the prognosis and severity of HF and also for monitoring response to treatment. Finally, the role of BNP in the outpatient cardiology or primary care office may be critically important in referring patients for echocardiography, titration of therapies, and to assess the state of neurohumoral compensation of the patient.[2]

Carvedilol improves survival?

Beta-adrenergic blockers reduce mortality in patients with chronic HF secondary to systolic dysfunction and should be added to treatment with diuretics and ACE-inhibitors. Several large clinical trials have shown a significant reduction in both morbidity and

mortality in HF patients when beta-blockers (including both carvedilol and metoprolol) are added to standard therapy.

Carvedilol (Coreg) is different than most other beta-blockers. It blocks beta-1 and beta-2 receptors and also inhibits alpha-1 adrenergic receptors, resulting in a reduction of vascular resistance while metoprolol has a high specificity for beta-1 receptors. Carvedilol decreases insulin resistance—metoprolol does the opposite. In addition carvedilol has anti-oxidant properties that may have some beneficial effects on endothelial dysfunction and apoptosis, mechanisms that could be important in the progression of chronic HF.[3] These additional properties, plus improved mortality benefits in the major trials, led to speculation that carvedilol could be more effective than other beta-blockers in the treatment of HF—thus the COMET trial.

The **C**arvedilol **O**r **M**etoprolol **E**uropean **T**rial (**COMET**) was designed to directly compare the effects of carvedilol and metoprolol on mortality and morbidity in patients with mild to severe HF.[4] "The results suggest that carvedilol 25mg bid used for the treatment of HF, in patients optimally treated with diuretics and ACE-inhibitors, has a significantly greater beneficial effect on survival than metoprolol 50mg bid. The absolute reduction in mortality over 5 years was 5.7%," say the investigators.

Many experts in the field have voiced objections over the dose and formulation of metoprolol used—metoprolol 50mg twice daily—saying that this is not an optimum dose of metoprolol and the superior effect of carvedilol in the trial could have been caused by a greater effect on beta-1 blockade alone. Since the pathogenic effects of increased sympathetic activity to which the myocardium is subjected in HF are largely beta-1 mediated, the question of dose has to be seriously considered…i.e. the small reductions in heart rate and blood pressure with carvedilol over metoprolol in COMET may be important. This camp of physicians is basically saying that all that COMET shows is that a higher dose regimen is better than a lower dose one. More study is needed.

My "take-home message" from COMET is to choose one of the two drugs approved for HF that have proven effects on mortality and morbidity—carvedilol or metoprolol CR/XL (Toprol XL)—and to give them at the doses used in the trials. This should result in a 30% to 35% decrease in mortality compared with no beta blockade and better results than with the immediate-release metoprolol 50mg bid. Patients on the immediate-release should be switched over to long-acting CR/XL metoprolol or carvedilol.

Carvedilol would be my first choice of the two because of its probable improved mortality benefits and possible other benefits. Retrospective analysis has shown beta-blocking agents with vasodilating properties (carvedilol) may provide additional benefits in diabetic HF patients because they improve insulin sensitivity and vasorelaxation.[5] Carvedilol is also proven beneficial at some of the lower doses.

Sparing a little could save a lot…Importance of aldosterone blockade

ACE inhibition and beta-blockers are the therapy of choice in patients with LV systolic dysfunction and HF but mortality and morbidity still remain high. Alternative therapies are needed. In 1999, results of the **R**andomized **AL**dactone **E**valuation **S**tudy (**RALES**), showed that aldosterone blockade with spironolactone added to ACE inhibitor therapy could reduce mortality in severe HF patients.[6] Only 10% to 11% of patients were receiving beta-blockers.

Eplerenone (Inspra) is a selective aldosterone blocker that is a "cleaner safer" version of spironolactone. It blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors, resulting in less impotence and painful gynecomastia. Findings from the **EP**lerenone Post-AMI **H**eart Failure **E**fficacy and **SU**rvival **S**tudy (**EPHESUS**) showed that treatment with eplerenone in addition to optimal therapy early after MI in patients with LV dysfunction and mild HF reduced overall mortality by 15%.[7] This was a randomized placebo controlled trial in over 6600 patients using eplerenone in a starting dose of 25mg, titrated to a maximum of 50mg per day, versus placebo. At baseline, 75% of these patients were on beta-blockers and 87% were on ACE inhibitors.

EPHESUS is a "grand slam"—extrapolating the results of RALES—documenting that aldosterone blockade improves outcomes and should be a standard part of the treatment program for all patients with HF secondary to LV systolic dysfunction (mild to severe). In addition, the 15% reduction in mortality occurs on top of the reductions provided by ACE inhibitors and beta- blockers.

Another recent retrospective study—therefore not conclusive—from the **S**tudies **O**f **L**eft **V**entricular **D**ysfunction (**SOLVD**) data base, concludes that the use of potassium sparing diuretics is associated with reduced risk of death from hospitalization, progressive HF or all-cause or cardiovascular death, compared with patients only taking a non-potassium sparing diuretic.[8]

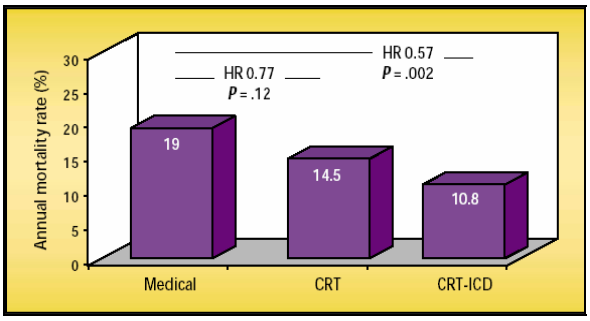
Caution is urged in prescribing aldosterone blockade for patients with elevated potassium or creatinine. ***The benefits of adding an aldosterone antagonist to usual standard therapy in patients with systolic HF is worth the extra effort of close monitoring of potassium and renal function that is recommended for everyone.*** An editorialist notes that there is no evidence that eplerenone is more effective than spironolactone and should not have preferential status as first therapy in these patients.[9] Rates of hyperkalemia are similar and cost will be higher; balanced against the improved side effect profile.

CRT limits mortality from progressive HF

Simultaneous pacing of the left and right ventricles, cardiac resynchronization therapy (CRT), which helps to get all cardiac cylinders "firing together", has been shown to improve cardiac function and quality of life in patients with chronic HF and ventricular dyssynchrony caused by intraventricular conduction delay.

Results of the **M**ulticenter **I**nSync **RA**ndomized **CL**inical **E**valuation (**MIRACLE**) study indicate that CRT improves a broad range of measures of cardiac function and clinical status in patients with moderate-to-severe heart failure and a prolonged QRS interval. Cardiac resynchronization reduced the degree of ventricular dyssynchrony (as evidenced by a shortened duration of the QRS interval). This effect was accompanied by an increase in the left ventricular ejection fraction, a decrease in the left ventricular end-diastolic dimension and decreased mitral regurgitation. When compared with the control group, the cardiac-resynchronization group had significant improvements in functional capacity, clinical status, and quality of life. Resynchronization also enhanced both maximal and submaximal exercise capacity (assessed by a treadmill test and the distance walked in six minutes, respectively).[10] CRT not only increased the likelihood of clinical improvement, but also reduced the risk of clinical deterioration during the course of follow-up.

At the recent ACC meeting in Chicago, a morbidity and mortality trial of CRT, **COMP**arison of Medic**A**l, Resynchronizatio**N**, and Defibrillat**ION** Therapies in Heart Failure (**COMPANION**), appeared to confirm these findings and suggests a reduction in all-cause mortality, especially when CRT is combined with a prophylactic implantable cardiac defibrillator —ICD.



Preliminary results of the Comparison of medical therapy, pacing and defibrillation in chronic HF (COMPANION) trial.

Presently, ***CRT is indicated in Class III-IV systolic HF despite adequate drug therapy, with QRS duration of at least 120 msec.***

Conclusions:

The triage **BNP is the first point of care assay available to aid in the diagnosis of HF**. With appropriate cutoffs, a high degree of diagnostic sensitivity and specificity can be achieved. This should be useful in the emergency room setting as well as in the outpatient primary care or cardiology office. As always the physician must remember that the diagnosis of HF is not made solely on the basis of a laboratory test or an echocardiogram, but rather on clinical grounds; these tests are used to augment clinical judgment. Further study is needed to delineate usage for prognostication and titration of therapy in HF patients.

Beta-blockers have proven morbidity and mortality reductions of > 35%, when added to ACE inhibitor therapy for HF secondary to LV systolic dysfunction. Carvedilol 25mg bid has an improved survival advantage compared to metoprolol 50mg bid. More study is needed to determine if it is superior to metoprolol CR/XL in the appropriate study doses. **Based on COMET and its' other possible**

beneficial effects, carvedilol is recommended as the beta-blocker of choice for HF.

Aldosterone blockade adds further mortality benefit when added to standard HF therapy with ACE inhibitors and beta-blockade. **Based on EPHESUS plus RALES, aldosterone blockade is now recommended for all classes of HF secondary to LV systolic dysfunction (previously only Class IV).**

CRT has **proven to be an efficacious adjunctive device therapy to standard medical therapies for symptomatic heart failure in association with QRS delay.** The therapy improves symptom status and exercise duration, slows measures of disease progression, and improves hospitalization rate and mortality.[11]

How many drugs for HF?

1. ACE inhibitors: decrease mortality by > 20%.

	Start	Minimum	Goal
captopril	6.25mg tid	50mg tid	100mg tid
enalapril	2.5mg bid	10mg bid	20 mg bid
lisinopril	2.5mg/day	20mg/day	40mg/day
quinapril	5mg bid	10mg bid	20mg bid
ramipril	2.5mg/day	5mg/day	10mg/day

2. Beta-blockers: decrease mortality by another 30% to 50 % on top of ACE inhibitors.

	Start	Goal
Carvedilol**	3.125mg bid	25-50mg bid
Metoprolol CR/XL	12.5mg/day	150-200mg/day

** Beta blocker of choice

3. Aldosterone blockers: decrease mortality another 15% to 27% added to ACE inhibitor and beta-blocker benefits.

	Start	Goal
spironolactone	25mg/day	50mg/day
eplerenone	25mg/day	50mg/day

4. Digoxin: decreases morbidity and probably mortality at appropriate low doses.

	Start	Goal level
digoxin	0.125mg/day	0.5 to 0.8 ng/ml

5. Non-potassium sparing diuretics: as needed to decrease volume overload.

6-7. Aspirin and a statin: probably would be of benefit in these high-risk patients.

Patients who remain refractory to the above maximized treatment should be considered for more aggressive interventions (CRT-ICD in those with prolonged QRS) and/or cardiac transplantation.

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