ALLA RICERCA DI MARKER BIOLOGICI DELLO SCOMPENSO CARDIACO

Cristina Cornali
Caratteristiche per definire i Marker Biologici

- alta sensibilità
- alta specificità
- alta riproducibilità
- scarsa biodisponibilità
- fornire informazioni non facilmente rilevabili da un assessment clinico approfondito
- indipendente da caratteristiche demografiche
- disponibile in modo diffuso
- avere cutoff noti, che possano aiutare le decisioni cliniche
- buon rapporto costo-efficacia
In 1981, de Bold injected myocardial homogenates into nondiuretic rats. The atrial muscle extract increased sodium and chloride excretion 30-fold, along with an impressive increase in urine volume. By 1985, this same group had identified specific granules that secreted the peptide, now known as Atrial Natriuretic Factor or Peptide (ANP), and noted that the substance also had a hypotensive effect and an inhibitory action on renin and aldosterone secretion. Thus, the heart was behaving as an endocrine organ.

The investigators noted that the inability of the kidney to excrete sodium in chronic heart failure could be related to ANP and that the peptide might hold promise in the therapy for both hypertension and heart failure. Francis subsequently described the elevation of ANP early in heart failure and surprisingly in patients with asymptomatic left ventricular dysfunction.

In 1988, Sudoh from Japan, isolated an ANP-like peptide from porcine brain tissue that had similar properties to ANP but was distinct in its amino acid sequence, hence the name brain natriuretic peptide (BNP). These investigators suggested that in human disease, both ANP and BNP might perhaps have a dual mechanistic action in sodium and volume homeostasis. Now, the family of natriuretic peptides is made up of at least 4 distinct entities, each with its own biological effect.
**Produzione e metabolismo dei Peptidi Natriuretici**

- L’espressione genetica del BNP si ha sia a livello atriale sia ventricolare
- I peptidi natriuretici sono rilasciati dai miociti di tutte 4 le camere cardiache, in risposta allo stirament e distensione delle fibre muscolari cardiache
- Lo stimolo principale alla sintesi è l’aumentato stress della parete del ventricolo sinistro ⇒ NPs riflettono il grado di sovraccarico Vs
- Citochine proinfiammatorie possono up-regolare il gene per il BNP e aumentarne la secrezione
- BNP è eliminato sia attraverso la clereance renale sia da un sistema enzimatico e da recettori di clereance del tessuto adiposo e altri tessuti. NT-proBNP ha la sola eliminazione renale.

(Q J Med, 2008)
BNP is constitutively released from ventricular myocyte as a preprohormone (134 amino acids) → pro-BNP hormone (108 amino acids)
Metabolismo dei Peptidi Natriuretici

- SNS stimulation
- Cytokines
- Ischemia
  - CAD, severe LVH
- Inflammation
  - Atherosclerosis
- Drugs
  - β-blockers, digoxin
- Thyroid hormones
- Anemia

RV wall stress

LA wall stress

LV wall stress

Cardiomyocyte stretch

BNP gene expression ↑

preproBNP ↑

proBNP ↑

Serum BNP ↑

Serum NT-proBNP ↑

BNP clearance ↓

NT-proBNP clearance ↓

Renal failure

Other factors ???

Obesity

+ (?)

- (?)

+(?)

-
Azioni fisiologiche dei Peptidi Natriuretici

- Vasodilatazione (sistemica, polmonare e coronarica)
- Effetto natriuretico (per riduzione riassorbimento del sodio) e diuretico (per aumento flusso renale e filtrato glomerulare)
- Inibizione del sistema nervoso simpatico (riduzione livelli noradrenalina)
- Inibizione del sistema renina-angiotensina-aldosterone (per soppressione dell’aldosterone plasmatico)
- Inibizione dei sistemi delle endoteline, citochine e vasopressina
- Inibizione dei meccanismi fisiopatogenetici responsabili dell’ipertrofia e del rimodellamento ventricolare e vascolare (proliferazione di cellule muscolari lisce e fibroblasti)
- Effetto protettivo sulla disfunzione endoteliale secondaria al processo aterosclerotico
- Attenuazione Pressione di Incuneamento Capillare Polmonare (PCWP) e pressione arteriosa polmonare media

(Q J Med, 2008; Heart Lung, 2008)
### Differenze BNP e NT-proBNP

#### Table 2

Key distinguishing features of the ventricular natriuretic peptides

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BNP</th>
<th>NTproBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components</td>
<td>BNP molecule (32 amino acids)</td>
<td>NTproBNP (76 amino acids)</td>
</tr>
<tr>
<td>Biologically active</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 min</td>
<td>120 min</td>
</tr>
<tr>
<td>Clearance mechanism</td>
<td>Neutral endopeptidase, clearance receptors, and renal clearance</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>Stability in vitro at room temperature</td>
<td>4 h</td>
<td>Up to 72 h</td>
</tr>
<tr>
<td>(method-dependent; BNP degradation starts as soon as the sample is collected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved cut-offs for CHF diagnosis</td>
<td>&lt;100 pg/ml: no HF 100–400 pg/ml: “grey zone” &gt;400 pg/ml: HF</td>
<td>&lt;300 pg/ml: no HF Age: &lt;50, &gt;450 pg/ml: HF Age: 50–75, &gt;900 pg/ml: HF Age: &gt;75, &gt;1800 pg/ml: HF</td>
</tr>
<tr>
<td>Diagnostic assay</td>
<td>Point-of-care assay or newly laboratory assay</td>
<td>Laboratory assay and newly point-of-care</td>
</tr>
</tbody>
</table>

*(Intern J Cardiol, 2008)*
Differenze BNP e NT-proBNP

Although the levels correlate with each other, the individual values of the two NPs are NOT interchangeable. They have different half-lives, different modes of degradation, and most important, different ranges and cut-off values.

Steady-state levels of NTproBNP are as much as 4- to 6-fold higher than BNP because of different clearance mechanisms and other factors of the respective peptides, although both peptides are released in equimolar amounts in circulation.

There is a close correlation between NT-proBNP and BNP, BUT frequent discrepancies in individual patients also demonstrate that both markers are neither clinically nor physiologically completely equivalent.

BNP is more sensitive to acute hemodynamic changes than NT-proBNP due to its shorter half-life.
In addition, BNP has a higher accuracy for diagnosing cardiac edema in patients of 65 of age and older (because renal dysfunction, which is prevalent in the elderly, is associated with a more prominent increase in NT-proBNP levels as compared to BNP level).

NTproBNP appears superior to BNP for the evaluation of suspected acute HF in patients with preserved LV ejection fraction (diastolic HF). However, their similarities far outweigh their differences.
AIM: to determine whether there are differences among the 4 cardiac natriuretic peptides (ANP, pro-ANP, BNP, NT-proBNP) used in the evaluation of elderly patients with symptoms that might be associated with heart failure and to evaluate the prognostic power of the 4 peptides for cardiovascular mortality.

No significant gender differences could be found in 3 of the 4 peptides. In ANP, a higher plasma concentration was found in men. A significant correlation was found between age and BNP ($r=0.37; P<.0001$), and NT-proBNP ($r=0.45; P<.0001$) and NT-proANP ($r=0.39; P<.0001$).

No major differences were found between the ability of the peptides to identify the signs/symptoms of heart failure. Enlargement of the heart on chest x-ray was a strong predictor of increased plasma concentrations of all peptides, the strongest being NT-proBNP. BNP had the most prognostic information (HR for cardiovascular death: 5.97), and ANP had the least (HR for cardiovascular death: 3.18).
The cardiac natriuretic peptides, ANP, NT-proANP, BNP, and NT-proBNP, could act as markers for impaired cardiac systolic function in an elderly population, as they respond early to an increased stretch of the individual cardiomyocyte. Moreover, the peptides are economical alternatives or complements to Doppler echocardiography in evaluating patients with suspected heart failure.

In clinical practice, one important question concerning the use of cardiac natriuretic peptides is which biomarker is best in identifying patients with systolic dysfunction. The results from the ROC analyses show that 3 of the 4 peptides are almost equal in their ability to identify those with impaired systolic function according to Doppler echocardiography, and these peptides (BNP, NT-proBNP, NT-proANP) provided almost identical prognostic information, whereas ANP gave substantially less information.

(J Cardiac Fail, 2007)
Utilità dei Peptidi Natriuretici

- Differenziare le cause di dispnea in setting di emergenza
- Predire outcome avversi dopo ospedalizzazione per scompenso cardiaco (es. riammissione e mortalità)
- Predire mortalità intraospedaliera
- Guidare e monitorizzare l’efficacia terapeutica per lo scompenso cardiaco

BNP nel plasma si correla a pressione Vsin telediastolica, PCWP, pressione atrio destro, pressione arteriosa polmonare diastolica. I valori sono elevati non solo nello scompenso sistolico, ma anche nel diastolico.

(JAMA, 2009; Heart Lung, 2008)
Fattori che influenzano il metabolismo dei Peptidi Natriuretici

- ↑ espansione volume circolante
- ↑ aumento pressione intraventricolare telediastolica
- fluttuazioni circadiane
- ↑ intake di sodio
- farmaci (corticosteroidi, diuretici, ACE-inibitori, agonisti e antagonisti adrenergici)
- ↑ citochine proinfiammatorie
- ↑ ormoni sessuali femminili (concentrazione di BNP è di circa 1/3 maggiore nelle donne <55 anni)
- ↓ tessuto adiposo e obesità (nei soggetti obesi i valori di NP dovrebbero essere moltiplicati per 1.6-1.8)
- ↑ età (a causa della disfunzione renale e dalla fisiologica ipertrofia miocardica)

(Q J Med, 2008)
Causes of increased levels of brain natriuretic peptide in plasma

- Left ventricular dysfunction (systolic or diastolic)
- Hypertension (ventricular hypertrophy)
- Myocardial infarction
- Angina (unstable and stable)
- Myocarditis
- Primary pulmonary hypertension
- Pulmonary embolism
- Chronic obstructive pulmonary disease associated with pulmonary hypertension
- Acute respiratory distress syndrome
- Congenital heart diseases with pulmonary hypertension
- Arrhythmias
- Subarachnoid hemorrhage, transient ischemic attack, stroke
- Increasing age
- Renal failure
- Sepsis, septic shock
- Liver cirrhosis
- Hyperthyroidism
- Anemia

Situations with brain natriuretic peptide levels lower than expected values

- Obesity (body mass index $> 30$ kg/m$^2$) (increased clearance in adipose tissue)
- Acute pulmonary edema (lag in increase)
- Acute mitral regurgitation
- Mitral stenosis/atrial myxoma (preserved left ventricular function)
- Hypothyroidism

(Heart Lung, 2008)
Table 1
Summary of selected non-heart failure causes of amino-terminal pro-B-type natriuretic peptide (NT-proBNP) elevation: possible diagnoses

- Heart muscle disease
  - Hypertrophic heart muscle diseases
  - Infiltrative cardiomyopathies, such as amyloidosis
    - Acute cardiomyopathies, such as apical ballooning syndrome
  - Inflammatory, including myocarditis and chemotherapy
- Valvular heart disease
  - Aortic stenosis and regurgitation
  - Mitral stenosis and regurgitation
- Arrhythmia
  - Atrial fibrillation and flutter
- Anemia
- Critical illness
  - Bacterial sepsis
  - Burns
  - Adult respiratory distress syndrome
- Stroke
- Pulmonary heart disease
  - Sleep apnea
  - Pulmonary embolism
    - Pulmonary hypertension
  - Congenital heart disease

*(Am J Cardiol, 2008)*
Elevation of NPs levels in the context of non-HF situations should not be regarded as a false-positive result, and elevated NT-proBNP values should not be discarded without consideration of the serious adverse outcomes associated with their elevation.
The Task Force of the European Society of Cardiology has recommended since 2001 that a NP assay should be included in the first step of the algorithm for the diagnosis of HF as are ECG and chest X-ray.
ACCURATEZZA DIAGNOSTICA dei PEPTIDI NATRIURETICI
L’accuratezza nel diagnosticare lo scompenso cardiaco da parte del medico di emergenza = 60%
Trattamento inappropriato in emergenza = 32%
Diagnosi di scompenso cardiaco fatta dal medico di medicina generale viene confermata nel 34% dei casi

⇒ ospedalizzazioni inappropriate
⇒ uso di terapie potenzialmente dannose
⇒ aumentata mortalità

(Q J Med, 2008)
BNP < 100pg/ml ⇒ SC improbabile (sens. 90%; spec. 76%)
BNP > 500pg/ml ⇒ SC probabile
[> 400pg/ml]

NT-proBNP < 500pg/ml ⇒ SC improbabile
[< 300pg/ml; negative predictive value 98%]
NT-proBNP > 2000pg/ml ⇒ SC probabile
[> 900pg/ml; positive predictive value 76%]

Accuratezza diagnostica BNP (100pg/ml) = 83.4%
- Area Under the Curve = 91%
- Negative Predictive Value = 98%

Area Under the Curve NT-proBNP (900pg/ml) = 94%

(Q J Med, 2008; Anaesthesia, 2009)
## Optimal NT-proBNP Cut-points

### “Rule in”

<table>
<thead>
<tr>
<th>Age strata</th>
<th>Optimal cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All &lt;50 years (n=183)</td>
<td>450 pg/ml</td>
<td>97%</td>
<td>93%</td>
<td>76%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>All 50-75 years (n=554)</td>
<td>900 pg/ml</td>
<td>90%</td>
<td>82%</td>
<td>82%</td>
<td>88%</td>
<td>85%</td>
</tr>
<tr>
<td>All &gt;75 years (n=519)</td>
<td>1800 pg/ml</td>
<td>85%</td>
<td>73%</td>
<td>92%</td>
<td>55%</td>
<td>83%</td>
</tr>
<tr>
<td>Overall average</td>
<td></td>
<td>92%</td>
<td>84%</td>
<td>88%</td>
<td>66%</td>
<td>93%</td>
</tr>
</tbody>
</table>

### “Rule out”

<table>
<thead>
<tr>
<th>Rule out</th>
<th>Optimal cut-point</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out</td>
<td>300 pg/ml</td>
<td>99%</td>
<td>62%</td>
<td>55%</td>
<td>99%</td>
<td>83%</td>
</tr>
</tbody>
</table>
“THE GREY ZONE”

3.1.1. “Grey zone”
The grey zone is defined as follows:

<table>
<thead>
<tr>
<th>BNP [28]</th>
<th>NT-proBNP [27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>100–400 pg/ml</td>
<td>&lt; 50 years old 300 450 pg/ml</td>
</tr>
<tr>
<td></td>
<td>50–75 years 300–900 pg/ml</td>
</tr>
<tr>
<td></td>
<td>&gt; 75 years 300–1800 pg/ml</td>
</tr>
</tbody>
</table>

The grey zone is observed in 25% of dyspnoeic patients, 3/4 of whom have HF as the ultimate diagnosis. These patients usually have mild HF and a good prognosis.

The grey zone needs extra physician attention and ancillary testing. The grey zone levels are far more strongly associated with heart failure when concomitant clinical features are present, such as a history of heart failure, jugular venous pressure, and prior diuretic use.

(Anaesthesia, 2009; Europ J Heart Fail, 2008)
NP migliorano outcome e gestione dello scompenso cardiaco?

- Riduzione dei costi di gestione dei pazienti con dispnea nei reparti di emergenza (sia BNP sia NT-proBNP)
- Migliora l’accuratezza del processo decisionale medico
- Riduce il rischio diagnostico e terapeutico
- BNP riduce la necessità di ospedalizzazione (75 vs 85%)
- BNP riduce la degenza ospedaliera (8 vs 11 giorni)
- BNP riduce i costi intraospedalieri ($ 5410 vs $ 7264)
- BNP riduce mortalità a 30 giorni negli ultra-70enni con SC (9% vs 17%)
- NT-proBNP riduce la riospedalizzazione a 60 giorni (33% vs 51%)
- NT-proBNP riduce la necessità di accesso in servizi ambulatoriali dopo 60 giorni dall’ospedalizzazione ($ 5180 vs $ 6129)

(Q J Med, 2008)
BNP e ANZIANO
- i valori di NP aumentano con l’età, a causa della disfunzione renale, delle alterazioni strutturali cardiache parafisiologiche: ipertrofia e fibrosi miocardica, disfunzione diastolica
- BNP è più accurato del NT-proBNP, a causa della ridotta clearance nella persona anziana, ma studi negli ultra-75enni BNP e NT-proBNP hanno dimostrato lo stesso valore diagnostico (AUC 82% vs 84% rispettivamente)

**Cut-off proposti per l’anziano:**
- BNP < 250 pg/ml
- NT-proBNP

<table>
<thead>
<tr>
<th></th>
<th>&lt; 50 anni</th>
<th>50-75 anni</th>
<th>&gt; 75 anni</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-pro-BNP</td>
<td>450</td>
<td>900</td>
<td>1800</td>
</tr>
</tbody>
</table>

Sensibilità: 90%; Specificità: 84%
B-type natriuretic peptides for the diagnosis of congestive heart failure in dyspneic oldest-old patients

Chenevier-Gobeaux C, et al. (Clinical Biochemistry, 2008)

BNP and NT-proBNP both appeared to remain independently predictive of CHF, even in oldest-old patients. In oldest-old patients, optimum thresholds for the diagnosis of CHF were found to be higher:

<table>
<thead>
<tr>
<th></th>
<th>&lt; 85 anni</th>
<th>&gt; 85 anni</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>270</td>
<td>290</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1700</td>
<td>2800</td>
</tr>
</tbody>
</table>

This “grey zone” range was larger for both BNP and NT-proBNP in oldest-old patients.

<table>
<thead>
<tr>
<th></th>
<th>&lt; 85 anni</th>
<th>&gt; 85 anni</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>160-360</td>
<td>250-590</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>650-3500</td>
<td>1750-6000</td>
</tr>
</tbody>
</table>

No effect of renal function on their diagnostic accuracy (renal influence is less evident when patients are aged-stratified).
BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial.  

*Pfisterer M, et al.* *(JAMA, 2009)*

N.499 patients > 60 years (mean age 77 years); N.289 patients > 75 years  

**End point:** survival free of all-cause hospitalizations plus quality of life.

**Study strategy:**  
- **symptom-guided therapy** (as recommended by clinical practice guidelines) with a target of reduction in NYHA class to II or less  
- **NT-proBNP–guided therapy** to a BNP level of less than 2 times the upper limit of normal and NYHA class of II or less.

The primary end point of 18-month survival free of all-cause hospitalization was not significantly different between the 2 groups and included similar improvements in quality of life in both groups.  
In secondary analyses, the NT-proBNP–guided group experienced fewer hospitalizations for heart failure.  
Patients older than 75 years did not experience the same benefits of reduction in hospitalization for heart failure and in fact, had more adverse effects from uptitration.
BNP e OBESITA’
Circulating levels of both BNP and NT-proBNP are significantly lower in overweight and obese patients.

Potential mechanisms:

- Increased degradation
  - BNP is cleared by clearance receptor NPR-C, abundantly expressed in human adipocytes
  - BNP is degraded by neutral endopeptidases, abundantly secreted by human adipocytes
  - NT-proBNP is not cleared by NPR-C or neutral endopeptidases

- Reduced cardiomyocyte synthesis
  - Altered neurohormonal interactions
  - Sex steroid hormones (estrogens, androgens)

BNP retains its prognostic capacity despite relatively less circulating BNP in overweight and obese patients with HF.

BNP not only predicted ventricular filling pressures and functional class, but it also correlated with mortality.
BMI should be taken into consideration when interpreting NP results, and that diagnostic cut-points need to be validated for overweight and particularly obese individuals.

Unlike BNP cut points, the consensus-recommended age-adjusted NT-proBNP cut points to rule in HF and age-independent cut points to rule out HF in patients with acute dyspnea are equally useful for obese and lean patients. Thus, no adjustment of NT-proBNP thresholds for BMI is recommended.

Unlike BNP cut points, the consensus-recommended NT-proBNP cut point for prognostication in acute dyspnea (approximately 1,000 ng/L) is equally useful across all BMI categories, without the need for further adjustment for weight. However, other studies suggested a very low BNP cut-off level (<50 pg/ml) to rule out HF in obese patients (BMI > 35 kg/m2), or, for reasons of simplicity, it seems justified to conversely double the NP value of an obese patient to correct for the increased BMI.

(Am J Cardiol, 2008; Europ J Heart Fail, 2008)
BNP e INSUFFICIENZA RENALE
The studies on NPs did not include patients with stage 5 chronic kidney disease. Kidney disease reduces the usefulness of BNP testing in the diagnosis of HF. A higher BNP cutoff level is likely required for excluding HF in patients with estimated GFR < 60ml/min per 1.73m2.

Contributing factors for the markedly elevated BNP and NT-proBNP levels in patients with ESRD:
- LV structural and functional abnormalities
- LV hypertrophy.

NPs correlated with deteriorating and residual renal function, with 24-h urine production.

BNP is reduced by dialysis with both high- and low-flux dialysis membranes, NT-proBNP only by high-flux membranes.

NT-proBNP plays an important adjunctive role to echocardiography in early identification of peritoneal dialysis patients who are at risk for circulatory congestion.
Correlazione BNP e NT-proBNP con GFR:
riduzione GFR di 10ml/min/1.73m² ⇒ aumento di BNP di circa 20% e
⇒ aumento di NT-proBNP di circa 38%.

Nel paziente nefropatico, alte concentrazioni di BNP non corrispondono ad adeguati benefici in termini di vasodilatazione e diuresi, a causa di un relativo stato di deficit di BNP o insensibilità agli elevati livelli.

Un elevato BNP in pazienti con ESRD rappresenta un campanello di allarme per coloro che non avevano pregressa anamnesi di cardiopatia.

Un singolo cutoff di 1200 pg/ml per NT-proBNP ha il 92% di sensibilità e il 70% di specificità per diagnosticare lo scompenso cardiaco in pazienti con severa insufficienza renale.

BNP “rul-out” cutoff per pazienti con GFR < 60ml/min/1.73m² = 200 pg/ml (invece di 100 pg/ml).
Troponins and End Stage Renal Disease

Level of cardiac troponin are frequently elevated in the absence of acute coronary syndrome among patients with varying degrees of kidney disease. The pathophysiologic mechanisms are not clear (decreased clearance, subclinical myocardial necrosis or injury, LV hypertrophy). Troponin T is a promising risk stratification tool in the End Stage Renal Disease population and may help frame therapeutic decisions. The Food and Drug Administration and the Kidney Disease Outcomes Quality Initiative approved the use of Troponin T as a biomarker for mortality risk stratification in ESRD.

For patients who have ESRD and present with possible acute coronary syndrome, a dynamic change in cardiac troponins of >20% after presentation should be used to define acute coronary syndrome.

(J Am Soc Nephrol, 2008)
BNP e CARDIOPATIE
**Miocardial Disease**

NT-proBNP may be significantly elevated in a wide array of myocardial diseases, including:

- hypertrophic,
- restrictive
- inflammatory heart muscle diseases
- infiltrative cardiomyopathies, such as amyloidosis.

Elevation of NT-proBNP in hypertrophic cardiomyopathy is more associated with the severity of hypertrophy than the severity of obstruction.

Inflammatory states affecting myocardial structure and function may lead to elevations of NT-proBNP. This includes acute reversible cardiomyopathies, such as:

- apical ballooning syndrome
- infectious myocarditis
- toxic metabolic insults to the heart muscle, such as those related to cancer chemotherapy.

(Am J Cardiol, 2008)
**Atrial Arrhythmia**

Patients with atrial fibrillation (AF) have elevated circulating levels of NT-proBNP, even in the absence of HF or significant structural heart disease. The relation between AF and NT-proBNP levels appears strongest in patients without acute destabilized HF.

Elevations of NT-proBNP associated with AF likely represent atrial and/or ventricular release in response to the arrhythmia. Nonetheless, caution is necessary when interpreting elevations in NT-proBNP in patients with AF.

*(Am J Cardiol, 2008)*
Valvular Heart Disease

- Several studies now demonstrate an intimate relation between NT-proBNP elevation and symptom onset as well as prognosis in patients with asymptomatic aortic stenosis.

- NT-proBNP concentrations are consistently related to myocardial performance and survival for those treated surgically as well as those treated conservatively.

- In patients with mitral valve stenosis, the left ventricle is theoretically "protected" from volume or pressure load. However, concentrations of NPs still appear to be useful for tracking disease presence and severity. The mechanism of the elevation of NPs in these patients likely reflects both left and right atrial distention, as well as right ventricular pressure and volume overload caused by secondary pulmonary hypertension.

- The relation between mitral valve regurgitation and NPs is also well established.

(Eur J Heart Fail, 2008)
In patients with **unstable angina**, the BNP level was higher than that in patients with stable angina or in healthy patients. Reversible ischemia may increase left ventricular wall stress to cause an elevation of BNP level in circulation.

An elevated BNP level 48 hours after **myocardial infarction** seems to be a strong predictor of death or the reoccurrence of heart failure within 1 year.

NT-proBNP measurements reflected changes in right ventricular structure and function in patients with **pulmonary hypertension**. 

*(Heart Lung, 2008)*
**Differenti range terapeutici dei biomarker in diverse condizioni cliniche cardiologiche**

*(Intern J Cardiol, 2008)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>BNP (pg/ml)</th>
<th>NT-proBNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal echocardiogram</td>
<td>5–60</td>
<td>&lt;60 years: m: 5–100, f: 10–200 &gt;60 years: m:10–150, f: 25–500</td>
</tr>
<tr>
<td>[57,59,65,79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated left ventricular diastolic dysfunction</td>
<td>40–400</td>
<td>–</td>
</tr>
<tr>
<td>[59,83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction (LVEF &lt;30–35%)</td>
<td>40–500</td>
<td>40–1200</td>
</tr>
<tr>
<td>[10,71]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Heart failure</td>
<td>100–1000</td>
<td>100–10000</td>
</tr>
<tr>
<td>[24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic heart failure</td>
<td>200–800</td>
<td>100–6000</td>
</tr>
<tr>
<td>[59,68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease with normal LVEF</td>
<td>30 150</td>
<td>50 250</td>
</tr>
<tr>
<td>[64,114]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
<td>100–1000</td>
<td>100–2000</td>
</tr>
<tr>
<td>[42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure mitral regurgitation</td>
<td>20–100</td>
<td>–</td>
</tr>
<tr>
<td>[73,74]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated pulmonary hypertension</td>
<td>50–400</td>
<td>50–2000</td>
</tr>
<tr>
<td>[33,91]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BNP e SCOMPENSO CARDIACO DIASTOLICO
BNP levels are lower in patients with isolated LV diastolic dysfunction as opposed to those with LV systolic dysfunction. Nevertheless, BNP/NT-proBNP values are related to the severity of LV diastolic dysfunction.

A BNP > 200 pg/ml or an NT-proBNP > 220 pg/ml along with echocardiographic parameters can be used as criterion for the diagnosis of and a BNP < 100 pg/ml or an NT-proBNP < 120 pg/ml for exclusion of diastolic HF.

In patients with possible HF, BNP/NT-proBNP can help to rule out both systolic and diastolic HF using the same cut-offs. BNP/NT-proBNP can assist in the diagnosis of diastolic HF in patients with symptoms and signs of HF but normal systolic LV function.

The prognostic value of BNP/NT-proBNP in patients with diastolic HF is less clear.

(Intern J Cardiol, 2008)
BNP ed EMBOLIA POLMONARE
NT-proBNP concentrations are elevated in patients with increased right ventricular pressures, such as pulmonary embolism, and pulmonary arterial hypertension.

In patients with pulmonary embolism, echocardiographic studies have confirmed that NT-proBNP concentrations correlate with both echocardiographic and invasive parameters of right ventricular dysfunction.

Furthermore, it has been shown that elevated concentrations of NT-proBNP correlate with adverse clinical outcome in patients with pulmonary embolism.

(Am J Cardiol, 2008)
Studies have suggested that BNP or NT-proBNP (as cardiac troponin) were accurate in risk stratification for Pulmonary Embolism in a middle-aged population and had a high positive negative value for in-hospital death.

However, other studies did NOT show any prognostic usefulness. Thus, in clinical practice we do NOT recommended measurement of BNP or NT-proBNP level for each case PE admitted to an ED.

NP levels should not replace the standard diagnostic process when pulmonary embolism is suspected; it is elevated in ~30% of patients and is associated with a worse outcome, especially when it occurs in the presence of elevated troponin levels.

(Q J Med, 2008; Europ J Heart Fail, 2008)
BNP e VALUTAZIONE PERI-OPERATORIA
B type natriuretic peptide – a diagnostic breakthrough in peri-operative cardiac risk assessment?
Rodseth RN. (Anaesthesia, 2009)

The traditional model of the pathophysiology surrounding peri-operative cardiac events has focused on the classic supply/demand ischemia hypothesis. The concept of the myocardium at risk of failure due to increased metabolic demand has not been explored.

There is a direct association between increasing level of BtNP and risk of post-operative cardiac events. Pre-operative BNP level > 40pg/ml was associated with a 5-fold increase in the risk of developing new ECG abnormalities or a raised post-operative cardiac troponin. Increased post-operative NT-proBNP above 860pg/ml identified patients who sustained a cardiovascular event. A significant rise in postoperative BtNP may identify patients who are unable to cope with the myocardial strain imposed on them and are undergoing a degree of myocardial decompensation.
B type natriuretic peptide – a diagnostic breakthrough in peri-operative cardiac risk assessment?

*Rodseth RN.*

(Anaesthesia, 2009)

<table>
<thead>
<tr>
<th>BNP Level</th>
<th>Risk of major adverse cardiac events</th>
<th>Risk of cardiac death, non-fatal myocardial infarction, acute pulmonary oedema and ventricular tachycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 300pg/ml</td>
<td>40%</td>
<td>81%</td>
</tr>
<tr>
<td>200-300pg/ml</td>
<td>4.9%</td>
<td>13%</td>
</tr>
<tr>
<td>&lt;200pg/ml</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

It is probably prudent to suggest that in patients with BtNP > 400pg/ml or NT-proBNP > 900pg/ml, elective surgery should be postponed until the patient’s medical treatment has been fully optimised.

A 70% increase in BNP levels and a 50% increase in NT-proBNP levels have been found to constitute a significant change from baseline in patients with stable cardiac failure. NT-proBNP level may be less sensitive to rapid haemodinamic shifts.
BNP use should be encouraged for the diagnosis, management and prognostication of, in particular decompensated cardiac failure, unstable coronary syndromes and aortic stenosis.

The role of BNP in patients presenting for low risk surgery has not been specifically examined but in asymptomatic patients is probably not indicated. Use of BNP measurement in those with good functional capacity (NYHA I) may not be justified. Whereas, in patients undergoing major or intermediate risk surgery, who are NYHA II or more, BNP offer a very attractive, relatively non invasive risk stratification tool.

BNP risk stratification will allow tailored intervention in the form of pre-operative optimisation as well as targeted intra and post-operative management.

A single pre-operative BNP level, or more ideally a pre and postoperative level, drawn as part of the routine peri-operative workup in patients presenting for major or intermediate risk surgery with a poor effort tolerance, may be useful integrated monitor of cardiac function. (Anaesthesia, 2009)
BNP e SEPSI
Levels of NT-proBNP have been shown to be highly variable and often markedly elevated in critically ill patients with septic and other noncardiac varieties of shock.

Pathogenetic mechanisms:
- myocardial depression
- increased wall stress
- right heart strain caused by ARDS
- altered myocardial contractility
- ventricular dilation

Levels of NT-proBNP appeared to peak 12–24 hours after admission to the ICU in most patients with sepsis.

(Am J Cardiol, 2008)
Sepsis-Associated Myocardial Dysfunction.
Diagnostic and prognostic impact of cardiac Troponins and Natriuretic Peptides

Maeder M, et al. (Chest, 2006)

50% of patients with severe sepsis or septic shock has any form of impairment of left ventricular systolic function:
- myocardial depression mediated by circulating depressant substances (TNF-alfa, IL-1B, IL-6)
- hypercirculatory state including decreased systemic vascular resistance and markedly increased cardiac index after fluid resuscitation.

Regarding the fact that the insertion of a pulmonary artery catheters (PACs) is an invasive procedure without proven survival benefit, and a comprehensive echocardiographic study requires a high degree of training and sometimes is not available within 24 h, a biomarker accurately detecting myocardial dysfunction and providing prognostic information in patients with sepsis would be of paramount interest (information about cardiac performance is needed for the selection of the most appropriate catecholamine regimen after adequate fluid resuscitation).
CARDIAC TROPONINS

- Mortality among troponin-positive patients was higher compared to that among troponin-negative patients, irrespective of the cause of troponin positivity.
- Patients with elevated troponin levels were more likely to be hypotensive, needed more therapy with vasoactive agents, received mechanical ventilation more often, and had longer stays in the ICU.
- Relationship between elevated troponin levels and left ventricular dysfunction assessed either by echocardiography or PAC.
- Duration of hypotension and the maximal number of vasopressor doses administered were found to be correlated to cardiac troponin levels.
- Elevated troponin levels have been shown to be related to the severity of the disease as expressed by global scores such as the APACHE II or SAPS II.

Elevated troponin levels in patients with sepsis indicate a higher severity of disease, the presence of myocardial dysfunction, and a worse prognosis.

(Chest, 2006)
Studies on the value of BNP testing in critically ill patients revealed conflicting results:

- BNP correlated neither with stroke volume nor LVSWI, nor pulmonary capillary wedge pressure (PCWP)
- no correlation between BNP level and cardiac index
- no significant correlations between PCWP and BNP have been found in ICU septic patients requiring invasive monitoring
- few data exist on the effect of fluid loading on BNP levels, and the relationships among right ventricular dimension, CVP, and BNP level, and thus fluid loading could still have an effect on BNP levels
- moderately elevated BNP levels in patients with ARDS.

(Chest, 2006; Heart Lung, 2008)
NATRIURETIC PEPTIDES

NT-proBNP might be a better, but by no means perfect marker, of myocardial dysfunction and prognosis in patients with severe sepsis and septic shock compared to BNP:

- NT-proBNP level was better correlated with LVSWI than BNP level in patients with respiratory failure of septic and nonseptic origin
- NT-proBNP may reflect hemodynamics and inflammatory stimuli over a longer period and thus might be more representative of the presence or absence of myocardial dysfunction and prognosis (an advantage of NT-proBNP over BNP might be its longer half-life).

(Chest, 2006; Heart Lung, 2008)
Schematic visualization of possible mechanisms leading to elevated cardiac troponin and BNP levels in patients with severe sepsis and septic shock.

ALI acute lung injury; IL interleukin; LV left ventricular; RV right ventricular; RVEDP right ventricular end-diastolic pressure; RVSWI right ventricular stroke work index; TNF tumor necrosis factor.

(Chest, 2006)
Mechanism of Troponin Release. Troponin leakage due to ischemia is possible even if myocardial necrosis does not occur: no differences in coronary blood flow; no myocardial lactate production; well-preserved myocardial oxygen metabolism.
Myocardial injury due to microvascular thrombosis and the presence of cytokines and procoagulant state could play a role.
In response to wall stress, intracellular signaling cascades are activated, resulting in myocyte apoptosis and thus troponin release. Troponin leakage following the up-regulation of inflammatory cytokines has to be considered as an alternative explanation.

Mechanism of BNP Release. Beyond left ventricular filling pressures, other stimuli might account for BNP release, including right ventricular strain, renal failure, catecholamine therapy, and cytokine up-regulation.

(Chest, 2006; Heart Lung, 2008)
BNP level does not sufficiently reflect LVEF and cannot replace invasive monitoring in patients with sepsis. Thus, a thorough echocardiographic evaluation is preferable to BNP testing.

The routine use of natriuretic peptides in patients with sepsis should be discouraged.

However, we recommend the use of cardiac troponins as a part of the monitoring of patients with severe sepsis and septic shock with respect to predicting prognosis and impaired systolic left ventricular function.

(Chest, 2006; Heart Lung, 2008)
BNP e BPCO
Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease.

Rutten FH, et al. (Eur J Heart Failure, 2007)

Studies designed to assess the diagnostic utility of B-type natriuretic peptides for detecting or ruling out heart failure in COPD patients are scarce.

N.200 patients with COPD (aged >65y).

Median values of all B-type natriuretic peptide assays differed significantly between those patients with and those without heart failure. Patients with systolic heart failure had higher natriuretic peptide levels than those with ‘isolated’ diastolic heart failure.

B-type natriuretic peptide levels were not influenced by the severity of COPD.

Different NT-proBNP and BNP assays are helpful diagnostic indicators for selecting patients who should undergo echocardiographic screening to detect previously unknown heart failure, in a population of stable elderly patients with a primary care diagnosis of COPD.
Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease.

Rutten FH, et al. (Eur J Heart Failure, 2007)

BUT, the overall diagnostic ability of both NT-proBNP and BNP are lower for detecting heart failure in stable patients with chronic dyspnoea and a diagnosis of COPD than in patients with acute dyspnoea presenting at the emergency department.

Due to low positive predictive values, the overall diagnostic ability of the BNP assays was moderate in identifying heart failure patients with LVEF 30–45% and poor for identifying those with ‘isolated’ diastolic heart failure.

Age- and gender independent ‘optimal’ cut-points (negative predictive values>85%):
- 125 pg/ml for NT-proBNP
- 35 pg/ml for BNP.
Few patients with moderate COPD have a BNP $> 100$ pg/ml or NT-proBNP levels $> 350$ pg/ml.

In patients with pulmonary hypertension and right ventricular dysfunction (e.g. in severe COPD, pneumonia, and primary pulmonary hypertension), NP levels are often in the grey zone and occasionally in the diagnostic zone for HF, reflecting the existence of major right ventricular stress and, in effect, right heart failure.

The accuracy of NP to diagnose HF is unchanged in the presence of pre-existing pulmonary disease. Monitoring of NP levels also improves patient management and reduces treatment costs.

(Europ J Heart Fail, 2008)
BNP in PAZIENTI AMBULATORIALI STABILI
For patients who have NP levels measured when stable, an increase in NP of 50% over baseline values accompanied by appropriate symptoms and signs confirms a clinical diagnosis of decompensation. It must also be considered that less than a 50% change in NP level may be within the range of biological variability in some patients, and not representative of a clinical event.

Optimal cut points for excluding HF in the office are
- BNP < 20 pg/ml
- NT-proBNP: 125 for <75y or 450 pg/ml for >75 years of age

[much lower than the exclusionary cut-points that should be used when investigating patients with acute dyspnoea].

*(Europ J Heart Fail, 2008; Intern J Cardiol, 2008)*
The recently updated European guidelines on chronic HF state that a normal or low (BNP or NT-proBNP) concentration in an untreated patient makes HF unlikely as the cause of symptoms.

However, optimal cut-off values are still under debate:
- for BNP, a cut-off value of approximately 70–80 pg/ml to rule out HF seems to be appropriate (although too many patients would fall in the grey zone between 40 and 400 pg/ml)
- for NT-proBNP, a cut-off of 125 pg/ml seems to be appropriate.

(Intern J Cardiol, 2008)
Applicazioni cliniche del BNP e NT-proBNP al di fuori del reparto di emergenza

(Intern J Cardiol, 2008)

1. BNP/NT-proBNP useful
   Evaluation of patients with suspected heart failure (HF) [9,22–24,55]
   Risk stratification in HF [25–28]
   Risk stratification in stable coronary artery disease [29,30]
   Risk stratification in pulmonary artery hypertension [31–33]
2. BNP/NT-proBNP possibly useful
   Guidance of medical therapy in HF [43,56]
   Risk stratification in the general population [34,35]
   Screening for left ventricular dysfunction in high risk populations [36,37]
   Diagnosis of coronary artery disease [38–41]
   Risk stratification in aortic stenosis [42]
3. BNP/NT-proBNP not useful
   Screening for left ventricular dysfunction in unselected populations [44,45]
   Hemodynamic assessment in HF [46–48]
4. Evolving applications of BNP/NT-proBNP testing
   Detection of cardiotoxic effects [49,50]
   Follow-up after cardiac transplantation [51,52]
   Selection of candidates for implantable cardioverter defibrillators [53,54]
BNP e MONITORAGGIO della TERAPIA
Some authors suggest to measure NP levels routinely at the time of admission and prior to discharge when optivolaemic status is achieved. Although, repeat NP measurements should be considered in the event of clinical deterioration or to evaluate adequacy of therapy, but is currently not indicated in the vast majority of inpatients with HF.

Knowing a patients' baseline optivolaemic NP level is likely to be important in monitoring the patient in the first 30 days after discharge.

A patient in whom NP has risen during hospitalisation or has dropped but is still in the 600–700 pg/ml range for BNP and >7000 pg/ml for NT-proBNP at discharge has an increased risk of cardiovascular events. Changing therapy based on measured NP levels has not yet been shown to be beneficial, but more aggressive monitoring and therapy may be wise.

From an economic perspective, there are currently insufficient data to determine whether regular assessment of NP levels is cost-effective for outpatient titration

*(Europ J Heart Fail, 2008)*
Why NP levels do not decline in some patients despite treatment:

1) a high NP level may actually be the patient's optivolaemic (dry) NP level due to persistent increased ventricular wall stress, even after resolution of acute episodes of volume overload.

2) worsening azotaemia from excessive diuresis may result in increasing NP levels

3) a patient with concomitant right-sided HF and significant ascites and/or oedema might diurese many litres before NP levels actually drop. This is likely due to mobilization of third-space fluid rather than lowering of cardiac filling pressures. Continuing diuresis and/or vasodilatation should eventually lower “wet” NP levels.

4) treatment does not effectively reduce central cardiac haemodynamics and therefore does not improve cardiomyocyte stress.

(Eur J Heart Fail, 2008)
BNP e STROKE
A significant relation for any of cardiac biomarkers to morbidity and mortality after stroke has not been found.

Elevated BNP levels in patients with subarachnoid hemorrhage have been shown to be associated with the severity of associated vasospasms, but also with measures of myocardial performance including regional wall motion abnormalities, impaired LVEF, diastolic dysfunction, cTnI elevation, and pulmonary edema. Release of BNP from the brain, or more probably from the heart, in subarachnoid hemorrhage is associated with more brain edema, cerebral vasospasm, and poorer outcome, and is a possible cause of cerebral salt wasting.

In patients with sepsis who have pathologies of the CNS (eg, meningitis, brain abscess, or previous head trauma) elevated BNP or NT-proBNP levels are difficult to interpret.

(Chest, 2006; Heart Lung, 2008)
NT-proBNP levels are frequently elevated in the setting of acute ischemic stroke.
Various mechanisms have been proposed, including increased secretion of NTproBNP for the vasodilatory modulation of cerebral ischemia or sympathetic nervous system activation resulting in higher arterial pressures and left ventricular wall stress. NT-proBNP predicts poststroke mortality.

Finally, NT-proBNP levels increased in patients with traumatic brain injury with increased intracranial pressure.

Uncertain prognostic value.

(Am J Cardiol, 2008)
BNP e DEPRESSIONE
Clinical and prognostic implications of self-rating depression scales and plasma B-type natriuretic peptide in hospitalised patients with chronic heart failure
*Parissis JT, et al.* *(Heart, 2008)*

155 pazienti ospedalizzati affetti da scompenso cardiaco (35-76 anni)
61.5% con sintomi depressivi
In 6 mesi 39.4% pazienti hanno avuto un evento clinico maggiore (morte od ospedalizzazione per scompenso cardiaco acuto)

In analisi di regressione logistica multivariata: la Zung self-rating depression scale e il BNP sono risultati indipendentemente associati agli outcome clinici.

Implicazioni fisiopatologiche:
- SC peggiora i sintomi depressivi
- Depressione si associa a un’iperattivazione dell’asse ipotalamo-ipofisi-surrene, aumenta il rilascio di ACTH, cortisolo e noradrenalina
- BNP influenza l’ipotalamo in reazioni emozionali, quali ansia
Biomarkers in Heart Failure

Eugene Braunwald  
(New England Journal of Medicine, 2008)

32 biomarkers divided into 7 categories:

- Inflammation
- Oxidative stress
- Extracellular matrix remodelling
- Neurohormones
- Myocyte injury
- Myocytes stress
- New biomarkers
BioMarker Cardiologici

- Atrial Natriuretic Peptide (ANP)
- Mid-regional pro-ANP
- Brain Natriuretic Peptide (BNP)
- Amino terminal pro-BNP (NT-proBNP)
- Mid-regional pro-adrenomedullin
- Copeptin
- Troponina
- Cystatin C
- Cysteine-proteinase inhibitor
- Growth differentiation factor-15 (GDF-15)

The combination of markers might be superior to the assessment of single markers.
An increased blood level of CRP is associated with a higher risk of cardiovascular events in patients with acute coronary syndromes and/or peripheral artery disease.

**CRP and Angina Pectoris**
- In patients with coronary heart disease (CHD) high CRP levels suggest a risk of recurrent ischemic events (a stronger predictor than the LDL cholesterol level).
- In patients with unstable angina or non-Q wave myocardial infarction, increased CRP at presentation correlates with an increased 14-day mortality even in patients without elevation of troponin.
- Elevated CRP levels reflect inflammation in the coronary artery than in the ischemic myocardium.

Data on CRP and myocardial infarction are more uncertain.

High level of CRP were evident in patients with in-stent stenosis, suggesting that an inflammatory process played an important role in the occurrence of restenosis.

CRP correlates with myocarditis, heart transplantation, aortic stenosis.
Anemia

It is still a matter of debate whether the anemia is a consequence of HF or vice versa or whether it just forms an independent co-morbidity. HF is a state of chronic inflammation where pro-inflammatory cytokines as IL-6 and TNF play a pivotal role; this in turn influences iron homeostasis.

Acido urico

A pathophysiological link between elevated uric acid and a large variety of detrimental processes (inflammation and increased cytokine production). Uric acid as a principal endogenous danger signal mediating immune response upon cell injury.

In chronic HF, high serum uric acid levels have been confirmed to indicate xanthine oxidase activation, which can lead to increased free radical oxygen load. Patients with HF in end-stage disease and cachectic patients have the highest uric acid serum concentrations, probably due to increased substrate influx from catabolic processes. Recently, high uric acid concentrations were shown as an independent predictor of a worse prognosis in patients with chronic HF.
Altri indicatori prognostici per lo Scompenso Cardiaco

- **Colesterollo**
  Lowering cholesterol beyond a certain limit might be detrimental. Cholesterol-mediated detoxification of lipopolysaccharide may, like anti-inflammatory cytokine IL-10, prevent the release of pro-inflammatory cytokines. This apparent paradox may have its basis in the dual effectiveness of statins that not only inhibit cholesterol synthesis but also possess so-called pleiotropic effects: anti-inflammatory effects and improvement in endothelial dysfunction, which is frequently present in patients with HF.

- **Cachessia**
  Histological skeletal muscle abnormalities relate to natriuretic peptide levels, which would be supportive of the muscle hypothesis in HF. Similar mechanisms are probably shared with development of cachexia in other chronic diseases.

*(Int J Cardiol, 2009)*
Conclusions

The natriuretic peptides have started to become an important asset in the field of both acute and chronic HF.

Usefulness:

- prediction of survival
- diagnostic value on top of the chest X-ray, the electrocardiogram, and Doppler echocardiography
- improved evaluation and treatment of acute dyspnea
- in emergency setting can decrease the costs of management and shorten time to discharge
- guidance in HF therapy, for example in adjusting the dose of ACE inhibitors, beta-blockers, and diuretics
- extending the use into other disciplines, for detecting early cardiac impairment in patients with cancer who receive specific cardiotoxic therapy.

(Int J Cardiol, 2008+’09)
Current HF guidelines recommend only the assessment of BNP and its precursor NT-proBNP for these purposes, while the assessment of ANP is considered less reproducible.

Moreover, besides HF, BNP/NT-proBNP seems to be useful in the following non-ED settings:

- risk stratification in stable CAD
- risk stratification in pulmonary artery hypertension

(Int J Cardiol, 2008+’09)
Algoritmo diagnostico per l’uso dei peptidi natriuretici in pazienti con dispnea

1. Unexplained dyspnea
   - History, physical examination, ECG, Chest x-ray
     - Cave: obesity: lower cut-offs
     - Renal failure: higher cut-offs

2. BNP/NT-proBNP testing
   - BNP<70 pg/ml or NT-proBNP<125 pg/ml, ECG normal
   - Underlying HF unlikely
     - Further work-up to evaluate other cause of dyspnea
       - Alternative cause of dyspnea identified
       - Dyspnea still unexplained
         - Consider

   - BNP<70 pg/ml or NT-proBNP<125 pg/ml, ECG abnormal (LVH, Q waves, marked ST/T changes, right-axis-deviation, left/right atrial overload)
   - Echocardiogram with focus on left ventricular systolic and diastolic function (including estimation of LVEDP by E/Ea measurement), valvular pathologies, and pulmonary artery pressure

   - If still unclear: consider stress test and/or assess the response to medical therapy

3. BNP>70 pg/ml or NT-proBNP>125 pg/ml
   - Diagnosis of HF established and underlying cardiac pathology determined
     - Specific work-up (e.g. stress test, myocardial perfusion imaging) and treatment (e.g. drug therapy, revascularization, valve surgery)

4. Obvious cause of dyspnea
   - E.g. large pleural effusion or other finding per se requiring cardiac work-up (e.g. atrial fibrillation)
   - Specific work-up and treatment (may also include an echocardiogram)