Acute heart failure: How to evaluate left ventricular filling pressure in practice?

Insuffisance cardiaque aiguë : comment évaluer les pressions de remplissage en pratique?

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Summary  Heart failure is one of the most frequent reasons for hospitalization due to a cardiac event. In most instances, the main difficulty is how to accurately evaluate left ventricular filling pressure. It can be evaluated clinically, biologically and invasively. Although historically, invasive management has been the reference, it is being used less and less frequently and expertise in the technique is being lost. This paper discusses the strengths and weaknesses of the different techniques for evaluating filling pressure in these patients, and the importance of this parameter for their optimal treatment.

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Background

The management of acute heart failure is dependent largely on clinical variables. The European Society of Cardiology Task Force on Acute Heart Failure has defined several different presentations (pulmonary oedema, cardiac decompensation, cardiogenic shock and hypertensive crisis), which have also been used in the recent recommendations for both acute and chronic heart failure, each of which has a specific evolution [1]. In the absence of easy standardization, there is a growing interest in biomarkers and haemodynamic variables, which allow straightforward diagnostic classification and may therefore guide therapy.

The use of biomarkers and echo-Doppler is a recent development, whereas pulmonary artery catheterization was developed years ago, when acute myocardial infarction was the main cause of acute heart failure. Pulmonary artery catheterization allows us to obtain the LV filling pressure when alteration of ventricular function differs from one side of the ventricle to the other; right ventricular filling pressure may be a misleading basis for estimation of LV filling pressure.

Physiology of natriuretic peptides

Natriuretic peptides have gained wide acceptance. ANP, which originates from the atrium, has a short half-life (around 3 min), is less sensitive than BNP for the diagnosis of heart failure and is no longer used in clinical practice. BNP, which is liberated from the ventricles, is almost absent in healthy individuals but increases significantly in patients with heart failure [2]. Both these natriuretic peptides are regulated physiologically; when increased left atrial pressure (for ANP) or diastolic LV wall stress (for BNP) is present, their secretion is increased and their plasma concentration rises. These peptides stimulate the generation of cyclic guanosine monophosphate.

In reality, BNP is synthesized as pre-prohormone BNP, which is cleaved into prohormone BNP (proBNP). ProBNP comprises the association of an N-terminal portion of 76 amino acids (NT-proBNP) with the active BNP molecule of 32 amino acids (Fig. 1). Both fragments (NT-proBNP and BNP) are released into the blood and, in theory, are cleaved before release and can each be measured in the plasma. However, this last event appears to be altered in heart failure, which means that assays may also measure the entire proBNP molecule, which is released into the blood in these patients [3,4]. The half-life of BNP is around 20 min, whereas that of NT-proBNP is longer (60–120 min). NT-proBNP is eliminated mainly by the kidney.

Factors other than heart failure that affect BNP plasma concentration

Heart failure is not the only circumstance in which BNP plasma concentration is increased [13]. An increase in right ventricular pressure triggers the release of BNP; pulmonary

Natriuretic peptides for the diagnosis of heart failure

Natriuretic peptide biomarkers are used in the diagnosis of acute heart failure; both BNP and NT-proBNP have been evaluated in patients admitted to an emergency department due to dyspnoea, and both have shown high diagnostic value for the confirmation or ruling out of heart failure (Fig. 2).

The largest study on BNP was the Breathing Not Properly Study, published in 2002, which included 1586 patients arriving at an emergency department with acute dyspnoea [5]; 47% appeared to have acute heart failure. Based on this study, a cut-off value of 100 pg/ml was proposed, with a diagnostic accuracy of 83.4%. The area under the curve of the receiver operating characteristic curve—a marker of diagnostic value—was 0.91 (1.0 being perfect). This diagnostic value was superior, and, more importantly, complementary to that of the clinical evaluation [6]. However, it may be wiser to consider this tool more as a continuum than as a black and white variable. Thus, a grey zone (ranging from 80–100 to 300–500 pg/ml) has been proposed, with suggested confirmation of heart failure above 300–500 pg/ml and suggested ruling out of heart failure below 80–100 pg/ml [1,7,8].

Similar findings have been obtained with NT-proBNP with an initial cut-off value of 450 pg/ml for patients less than 50 years of age and 900 pg/ml for patients above or equal to 50 years of age [9]. More recent studies favour ruling out heart failure when NT-proBNP is less than 300 pg/ml, whereas the diagnosis of heart failure is considered to be likely when NT-proBNP is greater than 450 pg/ml in patients less than 50 years of age, greater than 900 pg/ml in patients aged 50–75 years and greater than 1800 pg/ml in patients above 75 years of age [10]. The disadvantage of having different cut-off values according to age for NT-BNP and BNP is compensated for by the fact that values are similar in different centres, whereas the absolute value of BNP is dependent on the type of assay. The values indicated earlier for BNP are those obtained using the triage method.

There has been a lot of discussion regarding possible similarities in diagnostic accuracy between BNP and NT-BNP. Similar receiver operating characteristic curves were obtained in large independent multicentre studies in patients coming to an emergency department for dyspnoea (Fig. 2), and direct comparison of two assays in the same population indicated similar diagnostic values [11]. However, due to the importance of renal elimination of NT-proBNP, it has been suggested recently that a higher positive cut-off value of 1200 pg/ml should be used in patients with altered renal function (i.e. glomerular filtration rate less than 60 ml/min per 1.73 m²) [12].

BNP will be used as a generic term for BNP and NT-proBNP in the remainder of this paper.

Abbreviations

ANP atrial natriuretic peptide
BNP brain natriuretic peptide
EF ejection fraction
LV left ventricular
NT-proBNP N-terminal prohormone brain natriuretic peptide
proBNP prohormone brain natriuretic peptide
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Figure 1. BNP cleavage from NT-proBNP. This mechanism appears to be altered in heart failure.

Figure 2. Diagnostic value of BNP (left) and NT-proBNP (right) in patients with acute dyspnoea seen in an emergency department. The diagnostic values of BNP and NT-proBNP appear to be similar [5,9]. Diagnostic value of BNP (left) and NT-proBNP (right) in patients with acute dyspnoea seen in an emergency department. The diagnostic values of BNP and NT-proBNP appear to be similar [5,9]. (Left: Receiver- Operating-Characteristic curve for various cutoff levels of B-type natriuretic peptide [BNP] in differentiating between dyspnea due to congestive heart failure and dyspnea due to other causes. Right: NT-proBNP was highly sensitive and specific for the diagnosis of acute CHF, with a highly significant area under the curve. A strategy of partitioning patients in age categories of < 50 and ≥ 50 years (with cutoffpoints of 450 and 900 pg/ml, respectively) was optimal, with areas under the curve of 0.98 and 0.93, respectively [p < 0.0001 for the two categories].
embolism and other aetiologies of pulmonary arterial hypertension are therefore responsible for increased BNP plasma concentrations, which even carry a prognostic value in acute pulmonary embolism [14–16]. BNP plasma concentration also increases in response to ischaemia and conveys prognostic information during acute coronary syndrome [17]. Lastly, BNP plasma concentration appears to increase during sepsis, possibly as a result of LV systolic function depression [18].

Body mass index also alters BNP plasma concentrations, which are lower in obese patients with heart failure than in non-obese patients during acute decompensation and chronic patients (for heart failure of similar severity) [10,19]. It also appears that patients presenting very early after the acute onset of pulmonary oedema (‘‘flash’’ pulmonary oedema) may have normal BNP plasma concentrations despite clear pulmonary oedema [7]; out of 14 patients arriving within 4 hours of pulmonary oedema onset, four had BNP plasma concentrations less than 100 pg/mL, and 10 had BNP plasma concentrations greater than 300 pg/mL, indicating that BNP plasma concentration is not a good indicator of acute heart failure decompensation in this setting.

The measurement of BNP plasma concentration cannot therefore be considered to be an absolute tool for the diagnosis of heart failure in patients, but it complements the information provided in clinical evaluation.

**Practical use of BNP**

Whatever the limitations of BNP measurement for the diagnosis of heart failure in the emergency department in dyspnoeic patients, its benefit has been established firmly by a randomized trial comparing the evolution of patients arriving with dyspnoea who were managed either with the information that heart failure was likely (if BNP > 500 pg/mL) or unlikely (if BNP < 100 pg/mL), or with no additional information (BNP between 100 and 500 pg/mL); the BNP plasma concentration was made available within 15 min [8]. Compared with the group of patients in whom BNP measurement was not used, the time to treatment was shorter (63 min versus 90 min), the time to discharge was shorter (8 days versus 11 days) and the rates of hospital and intensive care unit admissions were decreased (from 85 to 75% and from 24 to 15%, respectively). This benefit was not negated by an increase in mortality, either during hospitalization (6% versus 9%) or after 30 days (10% versus 12%), nor by an increased rate of readmission at 30 days.

**LV end diastolic pressure**

**Estimation with BNP**

Because the stimulus for BNP secretion is LV end diastolic stress rather than end diastolic pressure, a close correlation between LV filling pressure (LV end diastolic pressure or pulmonary artery occlusive pressure) and BNP plasma concentration is not expected (Fig. 3) [20]. In fact, many studies have confirmed the loose relationship between these two values and, as a consequence, between the variation in LV filling pressure and the variation in BNP plasma concentrations [21–23]. There is, nevertheless, a relationship between the two values: BNP plasma concentration decreases in patients when pulmonary occlusive arterial pressure decreases in response to treatment. This association appears to be less obvious for NT-proBNP [24]. As a result, neither BNP nor NT-proBNP can be used to monitor filling pressures in patients with heart failure. This observation, combined with the ‘‘grey zone’’ in which the information given by the plasma concentration of BNP or NT-proBNP is moderate or null, has prompted a search for alternative ways of estimating LV filling pressures. Doppler echocardiography appears to be useful in this setting.

**Use of Doppler echocardiography**

Using Doppler echocardiography of transmitral flow, Logeart et al. found a restrictive filling pattern very useful for reclassifying patients who arrived very early (< 4 hours after onset of pulmonary oedema) and patients in whom BNP plasma concentration was within the grey zone [7]. Restrictive pattern was defined as E/A above 2 or E/A between 1 and 2 and a deceleration time of E wave less than 130 ms in patients in sinus rhythm, or simply a deceleration time of E wave less than 130 ms in those in atrial fibrillation. This pattern was present in 11 of 14 patients arriving within 4 hours and seven of 10 patients with acute heart failure with BNP plasma concentrations within the grey zone; the pattern was absent in 20 of 24 patients without heart failure with BNP plasma concentrations within the grey zone, including three in whom Doppler flow could not be recorded.

Another echocardiographic variable that could be valuable is the ratio of flow Doppler mitral E wave peak velocity and early diastolic velocity of the mitral annulus obtained by tissue Doppler (a mean of the values obtained at the septum and the lateral wall) [25]. This ratio is related to pulmonary capillary wedge pressure and its variation is also related to the variation in capillary wedge pressure, although the correlation is not strong enough to allow the use of one variable instead of the other; nevertheless, it enables patients with elevated pulmonary capillary wedge pressure (defined as > 15 mmHg) to be identified accurately. A cut-off value of 15 has been proposed for all patients, although whether patients with systolic dysfunction should be distinguished from patients with preserved EF is under discussion. The optimal value remained at 15 in patients with systolic dysfunction (EF < 50%), but a value of 11 was proposed in patients with preserved LV systolic function (EF > 50%) [22]. These data were obtained in patients with diverse pathologies, but similar values were obtained in patients with heart failure alone (11 for patients with an EF greater than 45% and 14 in patients with an EF less than 45%) [26]. Therefore, in clinical practice, Doppler mitral flow appears to be useful in association with BNP when the diagnosis remains dubious, but monitoring of instantaneous filling pressures with biomarkers appears to be ineffective.

**Prognosis of heart failure patients**

Monitoring may have other purposes, such as stratification of patient prognosis. The prognostic value of BNP or NT-proBNP plasma concentrations has been established in a wide-range
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Figure 3. Relationship between BNP plasma concentration and EF (upper left), end-diastolic pressure (EDP upper right), systolic wall stress (SWS lower left) and end-diastolic wall stress (EDWS, lower right). This last correlation is the strongest, suggesting that end-diastolic wall stress and not end-diastolic pressure or indices of LV systolic function can be evaluated with BNP plasma concentration [20].

of conditions; in patients with chronic heart failure, a high "baseline" BNP plasma concentration is associated with an increased risk of death [27]. The absolute value of BNP also carries prognostic information during and after decompensation, and its variation during hospitalization is also meaningful.

Cheng et al. reported that BNP plasma concentrations increased during hospitalization in patients who died, whereas they decreased in patients who were not rehospitalized or did not die [28]. In those readmitted, BNP plasma concentrations remained stable. The most valuable prognostic information appears to come from the BNP plasma concentration at discharge after treatment optimization [29]. This is also true for the pulmonary capillary pressure; its prognostic value is greater after optimization of medical therapy [30].

Other biomarkers have been shown to have prognostic value in patients with heart failure, either during decompensation or when in a stable condition. Troponin, C-reactive protein and interleukin-6, or more simple indexes such as creatinine or natremia, can also be used for this purpose.

Adaptation of heart failure therapy

Because of its prognostic value, the use of BNP plasma concentration to monitor therapy in patients with chronic heart failure has been proposed. As this is not the topic of this review, we have discussed the two existing studies briefly. The first study involved 69 patients with heart failure, very few of whom received beta-blockers [31]. A target NT-proBNP plasma concentration of less than 200 pg/mL was associated with a 65% decrease of hospitalization or death during a mean follow-up of 9 months compared with clinical follow-up alone. The Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) study included 220 patients and randomized patients to be followed up clinically or with BNP plasma concentration measurement, with a target concentration of less than 100 pg/mL [32]. This BNP-guided therapy was associated with a decrease in hospitalization or death of 50% (Fig. 4). Patients with BNP plasma concentration measurements received higher doses of all medication, indicating that the availability of a BNP plasma concentration is a motivating force in increasing the use of recommended
therapy. In reality, only 30% of the patients actually reached a BNP plasma concentration less than 100 pg/mL.

Very recently, a multicenter study reported that monitoring of Nt-BNP in patients with LVEF less than 45% did not change survival free of all-cause hospitalization in the whole population. However, in the subgroup of patients younger than 75 years, and in the subgroup of patients without more than one comorbidity, interaction suggested benefit on survival, hospital-free survival and heart failure hospital free survival. In this study, the aim was to decrease Nt-BNP to less than 400 pg/mL if above 75 years of age and less than 800 pg/mL if above 75 years of age [33].

Interpreting LV filling pressure, right heart catheterization

The cardiologist’s Holy Grail is to establish LV filling pressure. However, this variable is difficult to interpret for several reasons. Firstly, the estimation of LV filling pressure using a pulmonary artery catheter is subject to error, as it can only measure the pulmonary capillary wedge pressure, which is not always a good indication of end diastolic LV pressure. The difference between the two values increases as the stiffness of the left ventricle increases, i.e. as left atrial contraction contribution increases in the LV filling. Secondly, the optimal value for LV filling pressure may be difficult to define; in a stable patient with chronic LV systolic dysfunction, a baseline pulmonary wedge pressure of 15 mmHg or even 20 mmHg may be seen. Because lymphatic removal of exuding fluid may be greatly enhanced in this population, these high values may not be associated with pulmonary oedema, and trying to decrease this pressure acutely to a ’normal’ level would be a mistake. At the other extreme, an acute pulmonary oedema occurring in a patient with LV diastolic dysfunction but without chronic heart failure may occur with a much lower pulmonary capillary wedge pressure value. However, decreasing the LV pressure may lead to underfilling of the left ventricle and acute decrease of cardiac output. Thus, the interpretation of the absolute value of pulmonary artery capillary pressure obtained during acute haemodynamic distress and the choice of an optimal value for the patient are not obvious.

If LV filling pressure were the most important variable, its continuous measurement using a pulmonary artery catheter should facilitate optimal medical therapy. However, the benefit of pulmonary artery catheterization in the management of patients with acute heart failure has not yet been established. All the randomized studies, comparing care of patients with and without pulmonary artery catheterization, have been negative, reporting no benefit and only adverse effects (Fig. 5). These results were obtained in different populations, which were either heterogeneous (with shock or acute respiratory distress syndrome or both) and managed in intensive care units, usually by non-cardiologist physicians or more homogeneous, with pronounced heart failure and managed by cardiologists [34—36]. It is crucial that the physician is familiar with the technique, if it is to be used properly and with optimal benefit. Furthermore, full benefit cannot be expected to be obtained
when only occasional measurements are made, as the main advantage of this technique is the availability of repeated measures of haemodynamic variables. The use of a pulmonary artery catheter remains useful in expert hands to manage haemodynamically unstable patients who are not responding in a predictable fashion to traditional treatments, and in patients with a combination of congestion and hypoperfusion. In these cases, it is inserted to ensure optimal fluid loading of the ventricles and to guide vasoactive therapies and inotropic agents [37].

Repeated disappointment and technical difficulties, availability of alternative techniques and the progress made with echocardiography (including tissue Doppler imaging) are responsible for a decrease in the use of the pulmonary artery catheter. Besides, and probably most importantly, the importance given to haemodynamic optimization during acute heart failure decompensation is decreasing [38], because of the repeated observation during randomized trials in acute heart failure that haemodynamic improvement does not result in decreased duration of hospitalization or decreased mortality. This questioning of the value of haemodynamic variables during the acute phase of heart failure is reflected in the fact that even the regulatory agencies are shifting the endpoints from haemodynamic variables to functional ones (e.g. dyspnoea and well-being) and clinically relevant data (hospitalization duration and mortality) [39].

In fact, numerous variables are readily available in patients with heart failure during the acute phase of decompensation. Afterload can be established using arterial pressure, cardiac output can be evaluated with clinical variables and echocardiography (Doppler study of aortic flow), and right ventricular filling pressure can be gauged via clinical signs of right-sided congestion or the study of inferior vena cava on echocardiography. Only LV filling pressure is difficult to evaluate directly, and may differ from right ventricular filling pressure if a cardiopathy is localized to the left side, such as in acute myocardial infarction or LV hypertrophy in response to hypertension.

In conclusion, monitoring patients during acute decompensation is usually done on clinical grounds. Biomarkers may be of help for diagnostic purposes and determining patient prognosis, the most valuable information being probably derived after treatment optimization. Echocardiography Doppler and tissue Doppler are complementary tools. Haemodynamic monitoring is today seldom necessary in patients with acute heart failure. However, tomorrow, continuous haemodynamic monitoring through implanted leads may be available, and, if proved to be useful, may lead to reconsider our rules [40].

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