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Editorial

Natriuretic Peptides: Consensus Call for Use

Péptidos natriuréticos: consenso y uso necesarios

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Natriuretic peptides (NP) have become a laboratory tool with significant implications for the diagnosis, prognosis, and treatment of patients with suspected or established heart failure (HF). Their use affects various health care settings (clinics, emergency departments, inpatient wards, and laboratories) and a variety of different professionals, in both primary and specialized care. Therefore, the correct use of NP has implications for both the patient and the health care system, especially considering the epidemic nature of HF. Natriuretic peptides were included for the first time in clinical practice guidelines in 2001, and the first reference values for the diagnosis of acute HF were proposed in 2005. For the first time, the most recent guidelines include NP in the diagnostic algorithm of HF for both acute patients and outpatients (2012 European guidelines), with a class 1A recommendation for their use in HF diagnosis and prognostic assessment (2013 American guidelines).[1–3]

However, current NP use in medical practice does not reflect the international guideline recommendations. A survey by the Spanish Society of Cardiology in 2015, which included 107 public hospitals (with a catchment population of 31 million people), showed that NP testing was available in just 65% of emergency departments (66% of the population). One year previously, a survey by the Spanish Society of Emergency Medicine of 96 emergency departments showed that just 59% of hospitals had access to NP testing.[4] These data demonstrate the slow incorporation of NP into clinical practice, attributable to both the barrier imposed by the financial cost of their measurement and the fear of an indiscriminate or incorrect use due to lack of training. Therefore, the Spanish Society of Cardiology, the Spanish Society of Internal Medicine, the Spanish Society of Family and Community Medicine, and the Spanish Society of Emergency Medicine, which are formed by the professionals involved in the care of patients with HF, proposed the creation of consensus recommendations on the use of NP in patients with suspected or established HF. A working group of representatives from these societies, which included experts, went on to develop the final document.[5] The following paragraphs relate to the most important recommendations from the document. As there is currently no reason to justify the omission of NP from clinical laboratory testing, the first recommendation of the consensus document is that NP testing should be available in all health care settings, inpatient and outpatient, and for all professionals involved in HF care. However, indiscriminate use of NP testing is not justified either. The consensus establishes clear, concise recommendations on the settings and ways in which NP measurement should be used as a tool to help clinicians in their medical practice.

The use and appropriate interpretation of NP in clinical practice is possible only if the physician has the necessary knowledge regarding preanalysis (pathophysiology), analysis (methods), and postanalysis (interpretation and correlation with the clinical picture). Natriuretic peptide testing is used infrequently; this has probably led to its incorrect clinical use in many cases and to its not being incorporated into routine care. Therefore, one of the main recommendations from the consensus is the need for training on NP testing, even though these biomarkers are not novel technique. On this note, the document includes 10 points on both pathophysiology and methodology that requesting physicians should be familiar with if they wish to measure NP levels.

Natriuretic peptides are molecules with multiple biological effects on the cardiovascular system. They are classified as A-type, or atrial; B-type (BNP), or brain; and C-type, or endothelial. The most clinically useful type is BNP, which forms the focus of the document. Production of BNP is stimulated by increased stretching in myocardial cells and is proportional to the degree of increased intracardiac pressure. Thus, HF, be it with systolic or diastolic dysfunction, is the main disease in which BNP synthesis and secretion are increased. Synthesis and secretion occur rapidly after stimulation. Myocardial damage also leads to their secretion into the bloodstream. It is essential that clinicians understand the mechanisms of synthesis and secretion, as this helps them understand the presence of the 3 main forms of BNP that are detectable in blood: NT-proBNP (biologically inactive), BNP (biologically active), and the precursor molecule proBNP (which has 10% biological activity). Although there is equimolar release of BNP and NT-proBNP, they have different half-lives, so the

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concentration of NT-proBNP is higher than that of BNP. The consensus document includes a self-explanatory figure of the mechanism, to aid understanding.[5]

The different BNP can be measured by immunoassay, which may be completely automated, partially automated, or manual, such as the POC (point of care) methods. The document provides comparative tables with the characteristics of the main commercial methods available, and draws attention to the array of methods and molecular forms detected. This variety means that concentrations should always be expressed in pg/mL (equivalent to ng/L) and that values are not comparable between methods. The available immunoassays have a low "analytical variability". This allows the detection of differences between successive measurements attributable to changes in the patient's clinical status and not to analytical variability. However, blood concentrations of BNP have an intrinsic "biological variability" in both healthy individuals and in stable patients. This variability is greater for BNP than for NT-proBNP and greater when the time between measurements is short and the concentration is low. For instance, for weekly measurements in patients with stable HF, the "biological variability" of BNP can reach 50%, and that of NT-proBNP can reach 25%. This aspect, which is often unknown, is extremely relevant when it comes to interpreting serial values. Requests for repeat measurements should always be made once the clinical impression is established, as if not, increases and decreases may be falsely attributed to clinical changes. NT-proBNP has a low biological variability. In addition, the existing immunoassays for measuring NT-proBNP all use the same or similar antibodies and detect mainly NT-proBNP, not the other forms of BNP. For these reasons, NT-proBNP measurement has been expanded to a greater extent in clinical laboratories.

Levels of BNP and NT-proBNP increase with age and are higher in men than in women; levels decrease with obesity. In general, all cardiac and systemic diseases that involve increased myocardial cell stress or an increase in circulating blood volume lead to increased production and concentration of circulating BNP. This concept must always be borne in mind when interpreting results, and the clinical context of each individual patient must always be taken into account. Regarding extracardiac diseases, renal failure and pulmonary hypertension are the conditions that most significantly affect BNP concentrations. The document highlights the need to correlate NP concentration with each patient's clinical picture, which is the only way to ensure correct interpretation of the results.[5]

The recommendations on the clinical use of BNP form the core focus of the document. These recommendations are organized separately for the emergency (hospital) setting and the outpatient setting, and deal with BNP use in diagnosis, risk assessment, monitoring, therapeutic guidance, and the continuum of care. As a general recommendation, as with any diagnostic test, use of BNP testing should be: *a)* rational, based on the expected usefulness in terms of improved decision-making, diagnosis, or treatment, and *b)* included in consensus protocols formed by the participation of all departments involved in the care of patients with HF.

Use of BNP measurement to improve HF diagnosis has been extensively studied, and there is a vast amount of scientific evidence on the subject.[1,2] Three aspects bear mentioning: *a)* BNP measurement as an addition to clinical judgment improves diagnostic accuracy compared with a clinical diagnosis alone[6,7]; *b)* "dyspnea" is the main presenting complaint to which BNP measurements are applicable,[6,8] and *c)* the test is most useful for the exclusion of HF in patients with no previous diagnosis, or de novo cases.[9] Therefore, the main recommendation agreed by all the participating societies is that BNP measurement as a diagnostic tool should be available in all health care settings, including the emergency department and inpatient and outpatient settings. This recommendation is a priority, given that in Spain, BNP testing is not currently available in all health care settings and its availability should be considered a goal and a challenge for health care professionals, as it is supported by the current evidence from studies and guidelines. Once BNP measurement becomes widely available, the recommendations on its use are different for acute patients than for outpatients.

Natriuretic peptides should be measured when HF is suspected in a patient who presents with acute dyspnea and no previous diagnosis of HF. This recommendation is supported by the fact that, in this scenario, measuring BNP is cost-effective as it helps to improve diagnosis, progress more quickly to the appropriate treatment, and reduce costs and complications.[6,7,10]

In outpatients, that is, those who are not presenting acutely, there is less urgency and less evidence available. Therefore, the consensus is to use BNP on an individual basis. In any case, BNP testing is more useful when there is diagnostic uncertainty on the part of the clinician. Therefore, in outpatients, it is recommended to measure BNP when there is diagnostic uncertainty after the initial clinical assessment.[11,12] In both settings, rapid availability of the result is essential. For this reason, in the emergency department it is recommended to request the test on the first blood sample when the patient arrives, and in outpatients it is recommended that the result be available within 48 hours after the request. The consensus also gives priority to BNP over echocardiography for early exclusion, unless there is access to echocardiography results within 7 days, which usually occurs only in the setting of the cardiology department. It must be remembered that the diagnosis of heart failure may be made by a range of different professionals, most of whom do not have easy access to echocardiography. The document provides BNP reference levels for decision-making. Decisions must always be based on the individual patient.[6,7]

The consensus recognizes the usefulness of BNP in risk assessment and prognosis, as stated in the international guidelines. Natriuretic peptides are a quantitative marker of risk and it should always be borne in mind that the greater their concentration, the greater the risk of complications and the worse the clinical outcomes.[1–3,5,6] However, there is a consensus that the test should not be requested routinely for prognostic evaluation, but that it should be done to support clinical judgment and restricted to patients in whom the result will affect decision-making. On this point, the document contains a list of circumstances and scenarios in which such testing should be considered, such as when making the decision to send patients to the emergency department, to admit them to hospital, or regarding the type of care facility or choice of treatment in certain situations. The test should always be used to support clinical judgment, and the information must be adjusted for age and comorbidity. However, it is important to stress that BNP quantify cardiac stress and damage, and are therefore a cardiovascular warning sign. This information applies above all, but not exclusively, to HF; the presence of high concentrations in other disease states indicates increased cardiovascular stress and, consequently, a worse outcome (e.g, in sepsis). The document provides reference values above which the risk of serious complications increases significantly.

There is insufficient evidence on the use of BNP as a guide for treatment to recommend their routine use. However, as in risk assessment and prognosis, there is a consensus that such use is appropriate in certain circumstances. While individual studies have produced contradictory results, meta-analyses show the usefulness of BNP in optimizing pharmacological treatment and reducing adverse events in outpatients with HF, systolic dysfunction, and age < 75 years.[13,14] Given that these studies were carried out in specialized HF units, such use is recommended only for this

group of patients, in specialized HF units, and by staff with previous training in BNP use.

In addition to their use in guiding treatment, BNP can also be useful in monitoring patients with HF. Again, repeat measurements are not recommended for patient follow-up; their use in this context should be limited to situations where the results will affect decision-making. It should be noted that relative changes are always more useful than absolute changes, and that interpreting such changes will make sense only if there are previous values for comparison. The 2 main reference values are the value observed on arrival at the emergency department (the decompensated value) for hospitalized patients and the value when stable (the stable value) for outpatients. The decompensated value can be helpful as an indication of congestion resolution and when making the decision to discharge the patient from hospital, while the stable value can be useful for confirming suspected decompensation in an outpatient setting.[15,16]

In recent years, most clinical trials assessing new HF therapies have used elevated BNP values as an inclusion criterion. This reflects the importance of NP in the diagnosis of HF and the high probability that in the future, the indications for heart failure therapies will state a certain threshold NP level on the summary of product characteristics. This is another point that supports the need for these measurements to be available and for clinician training on the subject.

Lastly, a highly relevant aspect is the role of NP in the continuum of care of patients with HF. It is recommended that all values for each patient be included in their clinical records, discharge reports, and follow-up correspondence. Thus, if a patient is admitted to hospital, all the values obtained throughout their hospital stay should be documented. The NP level should not be seen as "a number" for one particular physician or specialist, rather as a piece of information relating to a patient that provides added value and will be useful for all the physicians involved in the patient's care. Sharing this information would contribute to improved patient care and increased understanding of NP.

The consensus document establishes 10 final recommendations that summarize the content. While this editorial reviews the main aspects of the consensus, it is recommended to read the full document. Only in that way will the ultimate goal be achieved: improved use of NP for enhanced care of patients with HF.

CONFLICTS OF INTEREST

J. Ordóñez Llanos declares having received grants for research or attendance at conferences and payments as a speaker or member of Advisory Committees from the main companies that sell natriuretic peptide measurement assays. A. Bayes-Genis declares having received grants for research or attendance at conferences and payments as a speaker from Roche Diagnostics. D.A. Pascual Figal declares having received research grants from Roche Diagnostics.

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