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B TYPE NATRIURETIC PEPTIDE SERVING CARDIOLOGY

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Summary

The use of biomarkers has significantly changed diagnostic thinking and more generally the management of emergency heart disease. But if the use of cardiac biomarkers in the management of heart disease in adults is no longer in doubt, there is currently no recommendation or expert consensus in children.

B-type natriuretic peptides have four missions:

- improve the diagnosis and, if their use is integrated into the decision-making algorithm in the face of dyspnea acute, and are also useful in the diagnosis of Acute and Chronic Heart Failure;
- determine the prognosis of heart failure;
- participate in monitoring and any heart failure patient should have a reference BNP dosage, its monitoring making it possible to identify patients at risk requiring a review of the therapeutic strategy;
- help optimize treatment.

Thus, provided they are confronted with the clinic and keep their limitations in mind, they constitute a useful guide in the management of patients with heart failure. Most learned societies have so far incorporated the use of these tools into recommendations for good clinical practice. They contribute to the emergency referral decision. The number of publications devoted to these biomarkers has grown exponentially, which denotes all the interest shown towards them. The few lines that follow will take stock of this thematic.

Keywords: Cardiac Biomarkers, Natriuretic Peptide B Type, Heart Failure, Adults, Children.

1. INTRODUCTION AND HISTORICAL CONSIDERATIONS

The history of cardiac markers begins in the 1950s at that time we were talking about completely non-specific cardiac enzymes such as Aspartate amino transferase 1954, and then more cardio-specific molecules appeared, namely Troponins and natriuretic peptides. It should be noted that with each “release” of a new biomarker, learned societies or the World Health Organization rushed to include it among the diagnostic criteria for myocardial infarction [1].

B-type natriuretic peptide (BNP), second member of the family to be discovered, was originally called brain natriuretic peptide because it was purified and sequenced from porcine brain [2].

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However, subsequent studies found that it is more highly concentrated in cardiac ventricles of patients with heart failure [3,4].Therefore, it is often described as B-type natriuretic peptide today.

Thanks to technological development, in recent years, many cardiac biomarkers have been developed to serve cardiology.

Heart failure (HF), defined as "the progressive mechanical inability of the heart muscle to provide sufficient blood flow for the body's needs", is, in industrialized countries, a public health problem due to significant morbidity and mortality.

If its prevalence is only 2% in the general population, it rises to more than 20% among those over 70, representing the leading cause of hospitalization.

Half of patients have a mortality rate of 50% at 4 years (50% at 1 year in cases of severe HF). Better pathophysiological understanding has led to the implementation of new therapies and diagnostic tools [5].

B-type natriuretic peptides (NPs) (BNP or NT-proBNP, N-terminus of BNP precursor) have a place in the diagnosis of acute or chronic HF, as well as in assessing HF prognosis and acute coronary syndromes. Several studies also highlight their potential interest in monitoring patients treated for chronic HF. However, learned cardiology societies (European Society of Cardiology in 2012) and the High Authority of Health (in 2010) recommend them in restricted clinical situations.

2. GENETIC ASPECTS AND LOCATION OF SYNTHESIS BNP:

BNP is part of the family of natriuretic peptides which have a cyclic structure which gives them their biological activity (Figure 1) [6]. Present in most mammals, the gene encoding BNP is located on chromosome 1 (1p36.2) and is composed of 3 exons and 2 introns in humans [7]. This gene encodes a protein of 134 amino acids (AA), pre-proBNP1-134. This precursor is transformed by enzymatic cleavage of its signal peptide (26 AA) into proBNP1-108 (108 AA), an O-glycosylated glycoprotein. A new maturation phase requiring the action of proteases, furin and corin, generates in an equimolecular manner on the one hand, a C terminal part, a holoprotein, BNP1-32 (32AA) and, on the other hand, a N terminal part, 76 AA glycoprotein, NT-proBNP1-76, with no known physiological action to date. There are several polymorphisms found in the coding region of human NPPB reported in the SNP database. Two, rs35690395 and rs35628673, result in synonymous amino acid residues. Four other SNPs result in changes in the sequence of preproBNP. One (rs5227) results in an R25L substitution of one amino acid before the signal cleavage site. Another mutation (rs5229) results in an R to H substitution at position 47 in the preprohormone sequence, which is the 21st amino acid of proBNP. Mutation rs5230 changes an M to an L at position 93 in preproBNP, corresponding to the 67th amino acid in proBNP. Mutation rs35640285 results in a V to F change at position 94, which is the 68th amino acid of proBNP. None of the above SNPs create changes in the

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sequence of the mature circulating 32 AA form of BNP. Like all natriuretic peptides, BNP is also cleared from the circulation by NPR-C[8].

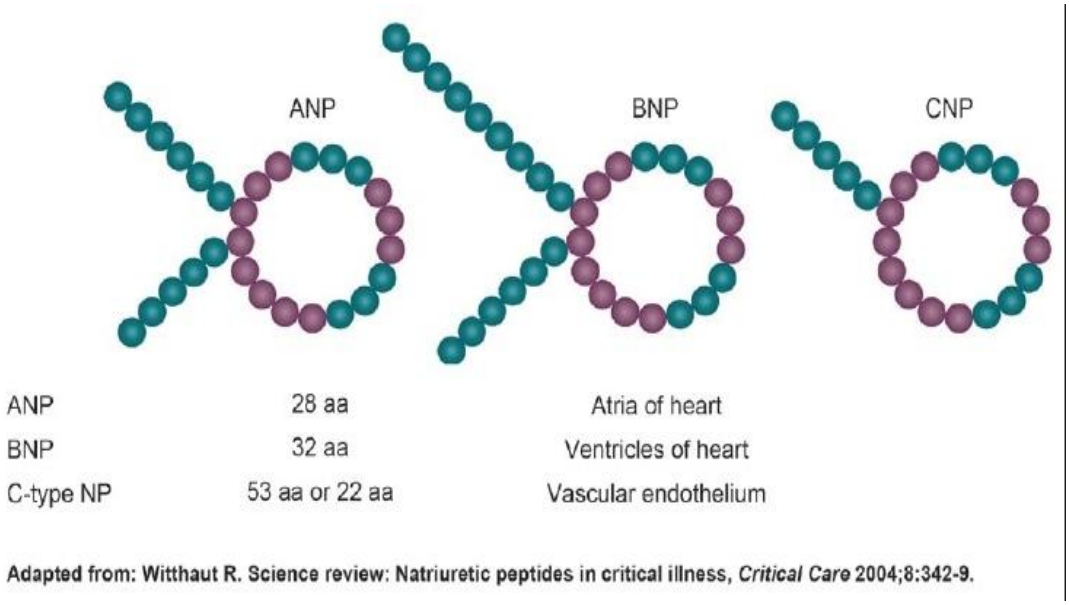

Figure 1: Structure of BNP [6]

3. PATHOPHYSIOLOGY OF B-TYPE NATRIURETIC PEPTIDES

Ventricular cardiomyocytes are the main source of circulating BNP in humans. The main stimulus for their synthesis and secretion is the stretching of myocytes in response to volume or pressure overload. They are secreted in the form of an inactive precursor of 108 amino acids (AA), ProBNP, which is split into an active peptide, BNP (C-terminal part of 32 AA) and an inactive glycopeptide, NT-proBNP of 76 AA, during its passage into the blood circulation. Not being stored in cardiomyocytes, their secretion only increases after de novo synthesis induced by stimulation as during the increase in left ventricular end-diastolic pressures during HF. ProBNP is the main circulating form; BNP and NT-proBNP are also present in native or truncated form after proteolysis of the N and C terminal (Figure 2) [9, 10]. The release of BNP into the blood flow by myocytes, essentially left ventricular, is exclusively regulated by the modulation of its synthesis at the transcriptional level, and not by the control of the exocytosis of proteins already produced and stored at the vesicular level. At the atrial level, storage vesicles are described, but participate little in the release of BNP in blood flow. Blood secretion involves neosynthesis of BNP/NT-proBNP during stimulation, and therefore a latency time for them to appear in the blood.

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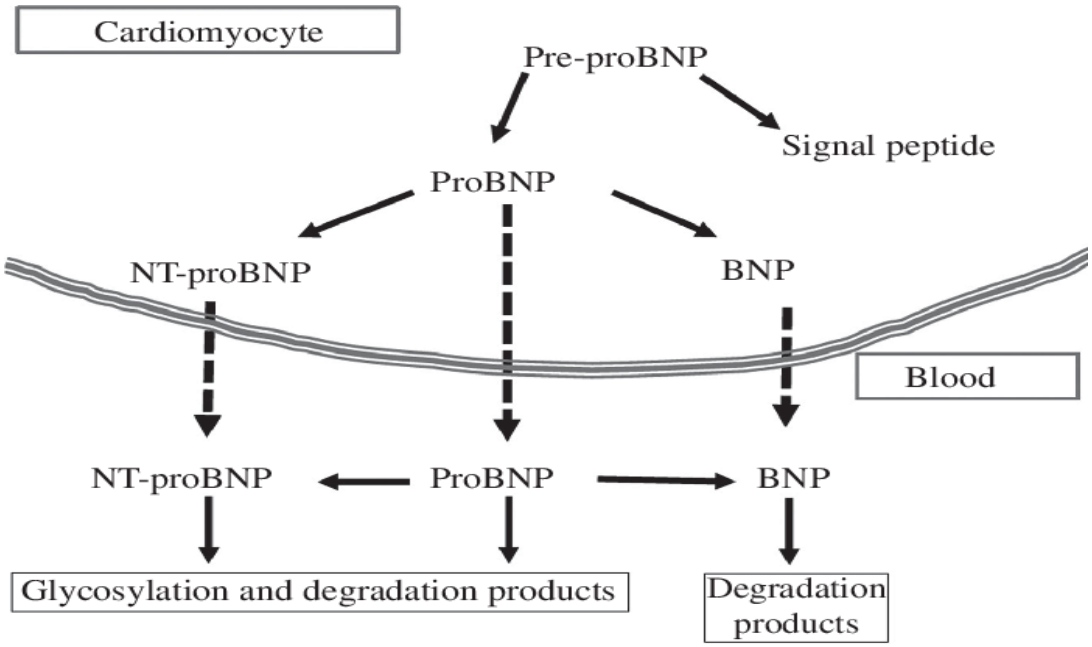

Figure 2: Schematic representation of biosynthesis, secretion and distribution of BNP [9]

4. MAIN ROLE OF THE BNP

It helps counterbalance the increase in pressure at the heart level.

It is vasodilator, natriuretic and diuretic. It inhibits sympathetic tone, the renin-system angiotensin-aldosterone and the synthesis of numerous vasoconstrictors (catecholamines, angiotensin II, aldosterone and endothelin 1), inducing a drop in blood pressure, particularly in cases of hypervolemia. It increases the glomerular filtration rate and reduces sodium reabsorption by direct action in the renal tubules (Figure3). It is eliminated either by endocytosis and proteolysis (thanks to a neutral endopeptidase – neprilysin – expressed on the membrane of many cells); or by glomerular filtration [11].

The plasma half-life is short, around 20 minutes; it is increased in the presence of neprilysin inhibitors, currently developed for therapeutic purposes in Heart Failure.

NT-proBNP has no known physiological action; it is eliminated by renal filtration, neutral endopeptidases having no action on it. Its half-life is therefore longer than that of BNP (60 to 120 min).

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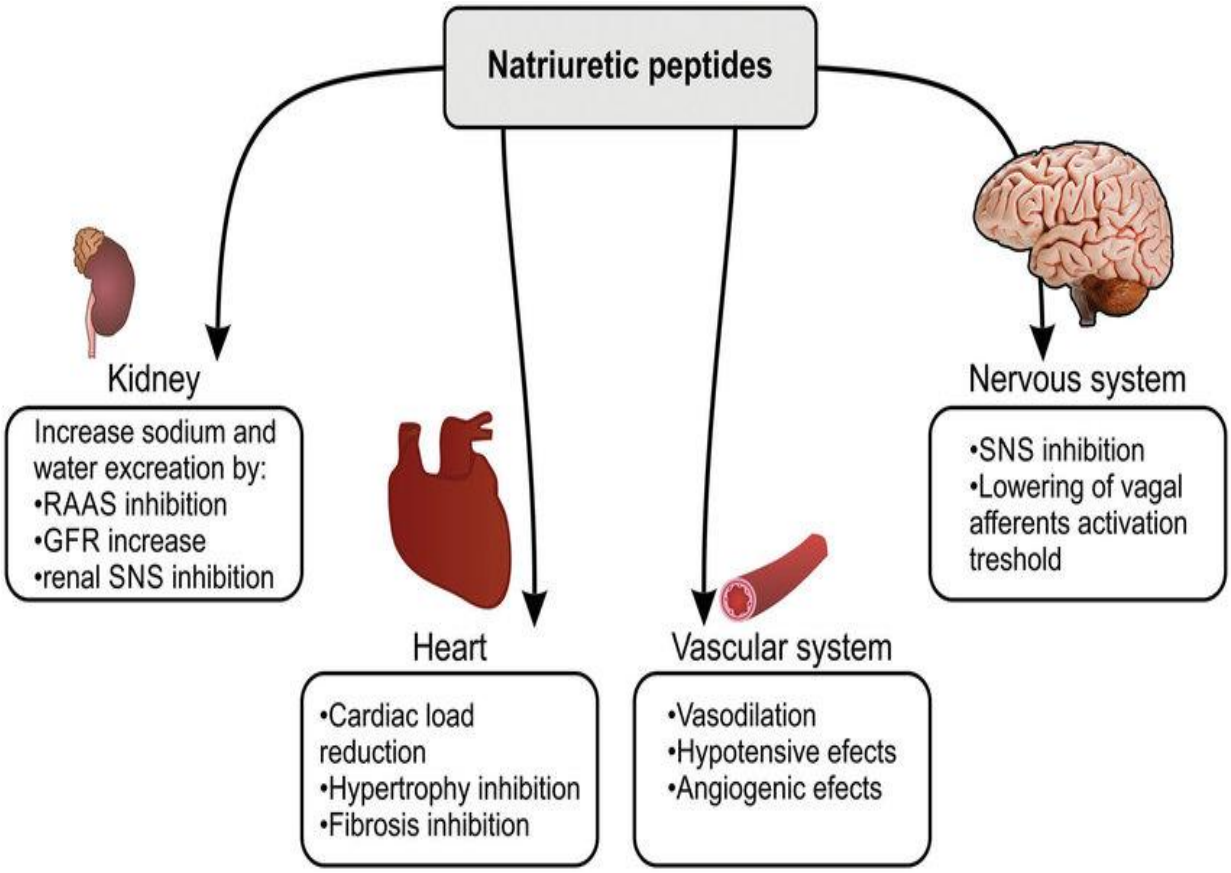

Figure 3: Physiological-effects-of-natriuretic-peptides [10]

5. ASPECTS ANALYTIQUES DES PEPTIDES NATRIURETIQUES DE TYPE B

Most assays (immunoassays) allowing rapid results to be obtained, suitable for emergency diagnosis. The in vitro stability of peptides has been a subject of controversy. BNP requires more pre-analytical precautions (dosage to be carried out less than 4 hours after collection) than NT-proBNP, which is more stable.

Current techniques recognize both BNP and its precursor proBNP. Similarly, the NT-proBNP assay detects both proBNP and NT-proBNP. In addition, more or less proteolyzed intermediate forms can be recognized, depending on the tests. Hence non-comparable results requiring that the dosage of the same peptide always be prescribed in the same laboratory [12].

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6. FACTORS INFLUENCING THE PLASMA CONCENTRATIONS OF B-TYPE NATRIURETIC PEPTIDES

They must be taken into account when interpreting the results:

6.1. Age, sex, body mass index: BNP and NT-proBNP increase after 45 yo, and are higher in women than in men and are inversely correlated with BMI (at rest and in young subjects, they may be undetectable). The fact that the 2 markers are lower is more in favor of a reduction in their cardiac release than an increase in their clearance.

Thus, threshold values should be lowered in cases of severe obesity [13-15].

6.2. Renal failure: the increase in BNP is moderate in patients with Renal Insufficiency in the absence of associated heart disease and therefore essentially reflects cardiac function. However, it is necessary

take into account the decline in renal function with age, and it seems reasonable to increase the threshold value for exclusion of acute heart failure to 200 ng/L in the event of a glomerular filtration rate (GFR) < 60 mL/ min/1.73 m2. On the other hand, NT-proBNP, whose clearance is mainly renal, is closely correlated with GFR, which complicates its interpretation in elderly subjects, especially since acute heart failure can itself lead to an increase in GFR. Serum creatinine due to decreased renal flow. NT-proBNP therefore appears to be a “cardio-renal” marker, unlike BNP which essentially reflects cardiac function [16].

6.3. Individual/ethnic variability: Within a given patient, significant variations occur from day to day and throughout the day.

Thus, during follow-up, the increases or decreases in BNP or NT-proBNP must be considerable (of the order of 80-100%) to be significant; Asian and Black African patients have higher values than Caucasians [13-15].

7. CURRENT GUIDELINES FOR THE INTERPRETATION OF B-TYPE NATRIURETIC PEPTIDES

If typical clinical picture of heart failure, cardiac ultrasound remains the key examination which allows a decision to be made. [17].

The recommendations of the High Authority of Health of 2010 and of the ESC of 2012 recommend the dosage of natriuretic peptides in the event of atypical symptoms which may suggest chronic heart failure or decompensation, as an aid to initial diagnosis (figure 4). Thresholds differ depending on the context. In the non-acute phase, they are 35 ng/mL for BNP and 125 ng/L for NTpro-BNP. For lower values and if the ECG is normal, ultrasound is not justified. If acute heart failure is suspected, values below 100 ng/L and 300 ng/L respectively allow this diagnosis to be excluded (negative predictive value of around 99%). For higher rates, confirmation by ultrasound is necessary [18].

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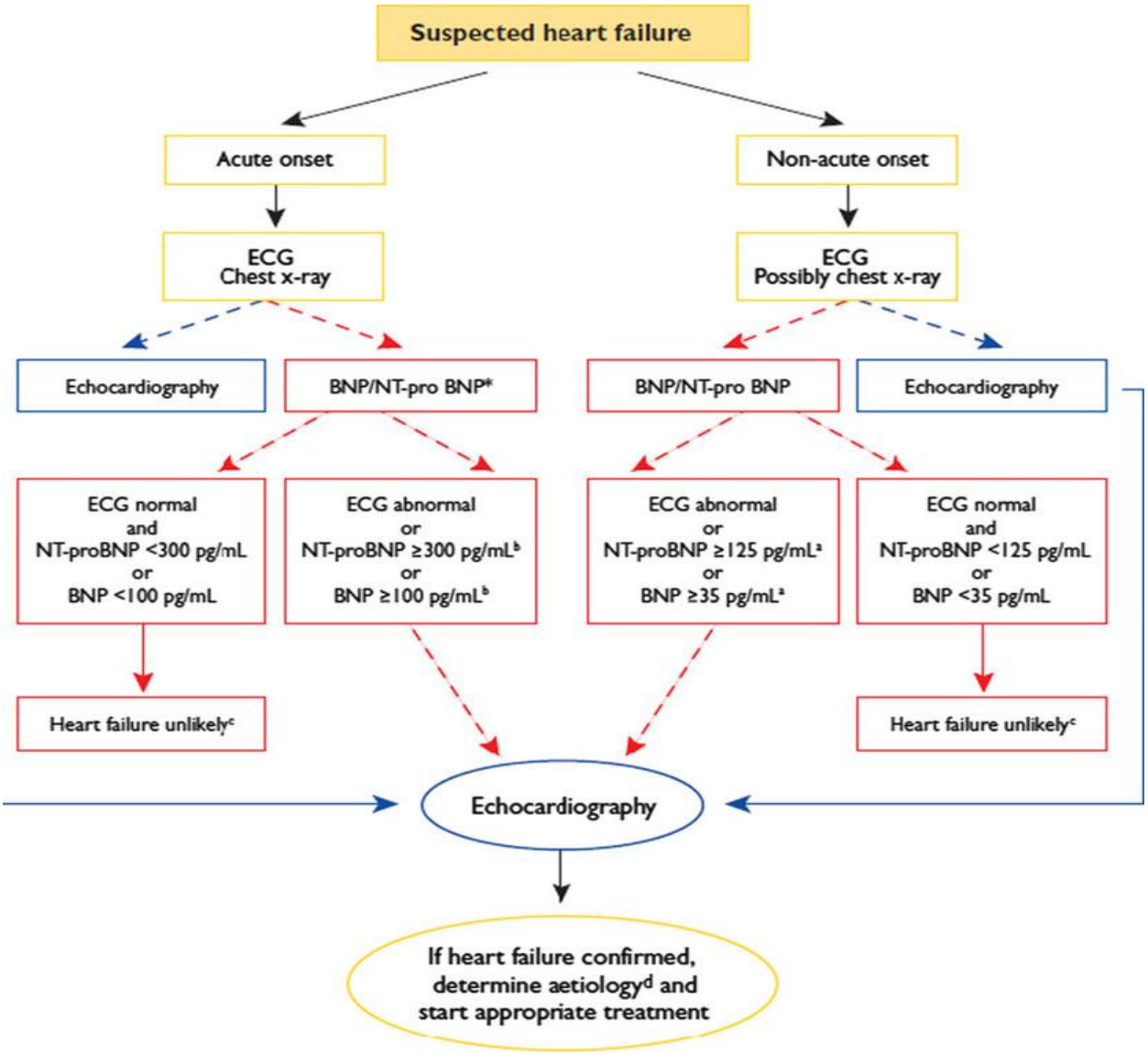

Figure 4: Diagnostic-flowchart-for-patients-with-suspected-heart-failure-showing-ESC 2012[17]

BNP and NT-proBNP measurements have been proposed as a prognostic biological tool [19,20]. but also for monitoring the treatment of HF because their concentration is associated with the prognosis and therapeutic success. This usage is currently not codified. Two different strategies have been proposed, with the objective of reducing mortality, rehospitalizations and increasing quality of life compared to follow-up.

Classic therapeutic intensification based on variation in NP concentration; adjustment of treatment according to a concentration objective to be achieved (100 pg/mL and 1,000 pg/ mL for BNP and NT-proBNP respectively).

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Patients whose monitoring includes the measurement of natriuretic factors would have more aggressive heart failure therapies, increased quality of life and improvement in cardiac function as demonstrated by ultrasound. The persistence of a high concentration of natriuretic factors in a person with cardiac failure must therefore encourage therapeutic intensification [21-24].

8. NEW INDICATION FOR B-TYPE NATRIURETIC PEPTIDES: ATRIAL FIBRILLATION

Atrial fibrillation (AF) is by far the most common arrhythmia observed by doctors.

In the United Kingdom, more than 700 patients from the British Black Country Atrial Fibrillation Registry (BBC-AF) who had no known AF underwent a seven-day outpatient ECG screening [25]. Of the 40 biomarkers and clinical parameters studied, which included male gender, advanced age and high body mass index, B-type natriuretic peptide (BNP) and fibroblast growth factor 23 (FGF -23) were found to be the most associated factors with AF significant, with an odds ratio of 1.293 and 1.667 respectively[25].

Another more recent study reveals that in patients with atrial fibrillation (AF), a high level of NT-proBNP is associated with excess mortality and a greater risk of stroke. And should therefore be taken into account in the decision to anticoagulate patients or not [26].

9. USEFULNESS OF BNP IN PEDIATRICS

In pediatric cardiology despite the absence of recommendations, cardiac biomarkers can prove useful in the diagnostic and prognostic process, particularly the measurement of BNP. One of the best indications in children is the differential diagnosis of heart failure of respiratory origi. There are few standards for children. The best known dates from 2009 and proposes several thresholds depending on age groups and sex in children and newborns [27]. A summary study identifies the diagnostic, prognostic and therapeutic monitoring interest of BNP in the cases of heart failure in children[28].

The measurement of BNP is indicated in the case of congenital heart disease, as a diagnostic biomarker, prognosis and monitoring in children presenting acute respiratory distress with cardiac malformations.

Several authors recommend the use of pulse oximetry to screen for congenital heart disease in neonatal and pediatric patients; the measurement of BNP can increase the precision of this screening for the diagnosis of malformations, especially in POCT - point of care testing. This bedside approach is easy to carry out, and is conducive to setting up a screening program.

Furthermore, in newborns with patent ductus arteriosus, the BNP assay is recognized as a marker for screening, monitoring and prognosis. Finally, BNP are very sensitive markers to any acute or chronic increase in pulmonary arterial pressure. They are therefore good markers of prognosis and monitoring in children with pulmonary arterial hypertension.

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They are also very useful in the early detection of myocardial toxicity to anthracyclines, in particular left ventricular failure in cancerous children taking doxorubicin.

10.THERAPEUTICS OF BNP

BNP levels is used in the clinic as a diagnostic indicator for heart failure, and synthetic forms (Nesiritide) have been approved in some countries for the treatment of heart failure [29].The extent of their usefulness, however, has come under question due to their limited renal actions, and trials are underway to determine the most effective use of these peptides.

11. CONCLUSION

The blood measurement of type B natriuretic peptides (NT-proBNP or BNP) has taken a prominent place as a tool for diagnosing heart failure, in cases of clinical doubt. These very sensitive markers are also useful for prognosis, monitoring and optimization of treatment of chronic heart failure patients.

In pediatric cardiology, there are numerous indications for the use of cardiac biomarkers, BNP, and there is an urgent need to establish recommendations in children, in particular for the dosage of BNP in cases of heart failure.

Conflicts of interest

No conflict to declare.

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