THE ROLE OF NT-PROBNP IN ASSESSING THE CONTROL OF DECOMPENSATED HEART FAILURE PATIENTS

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ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AHF	acute heart failure
ARB	angiotensin receptor blocker
AV	atrioventricular
BNP	B-type natriuretic peptide
b.p.m.	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCB	calcium-channel blocker
COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronisation therapy
CRT-D	cardiac resynchronisation therapy-defibrillator
CRT-P	cardiac resynchronisation therapy-pacemaker
CT	computed tomography
ECG	electrocardiogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
HF	heart failure
H-ISDN	hydralazine and isosorbide dinitrate
HUSM	hospital Universiti Sains Malaysia
i.v	intravenous
IABP	intra-aortic balloon pump

ICD	implantable cardioverter-defibrillator
LA	left atrial
LBBB	left bundle branch block
LV	left ventricular
LVEF	left ventricular ejection fraction
LVIDd	left ventricle internal diameter, diastole
LVIDs	left ventricle internal diameter, systole
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal B-type natriuretic peptide
NYHA	New York Heart Association
RCT	randomised controlled trial
TDI	tissue Doppler imaging
TOE	transoesophageal echocardiography
VP	velocity propagation

PERANAN NT-PROBNP DALAM MENILAI KAWALAN TERHADAP PESAKIT KEGAGALAN JANTUNG DEKOMPENSASI

ABSTRAK

Latarbelakang: Beberapa kajian telah menekankan peranan peptida natriuretik (BNP dan NT-proBNP) untuk mendiagnos, untuk menilai tahap keterukan dan prognosis, dan untuk mengawal kegagalan jantung dalam kalangan pesakit luar. Walaubagaimanapun, terdapat hanya sedikit kajian yang menunjukkan peranannya dalam menilai kawalan ke atas kegagalan jantung dalam kalangan pesakit yang dimasukkan ke hospital, dan kesannya dalam jangka masa pendek dan pertengahan.

Objektif: Untuk menilai peranan NT-proBNP dalam kawalan pesakit yang menghidapi penyakit lemah jantung dekompensasi akut dan hubungannya dengan ciri-ciri klinikal, hasil, penemuan ekokardiografik dan elektrokardiografi.

Metodologi: Pesakit yang dimasukkan ke hospital kerana mengalami penyakit lemah jantung dekompensasi akut telah menyertai kajian kohort prospektif menggunakan persampelan sistematik. Penilaian klinikal menyeluruh dengan menggunakan skor simptom dan tanda-tanda, NT-proBNP, ekokardiogram transtorasik and elektrokardiografi telah dijalankan semasa kemasukan dan discaj. Peristiwa berpenghujung (kemasukan semula untuk penyakit lemah jantung ataupun kematian) dalam 1 bulan dan 6 bulan selepas discaj pesakit diperhatikan.

Keputusan: Tiga puluh orang pesakit yang dimasukkan ke hospital kerana kegagalan jantung dekompensasi akut menyertai kajian, dengan purata skor klinikal 7.33 (1.47), median NT-proBNP (2470pg/L), dan purata pecahan pelemparan (EF) 38.48% (12.52) semasa kemasukan wad. Purata jangka waktu kemasukan adalah 4.83 hari

(1.74). Pada waktu discaj, purata perbezaan dalam simptom klinikal dan tanda-tanda adalah 3.13 (95% CI 2.68-3.57), EF -5.75 (95% CI -8.95, -2.55) dan perbezaan median untuk NT-proBNP adalah 595 (p value < 0.001), dan ianya menunjukkan peningkatan yang signifikan. Walaupun begitu, analisis data menunjukkan bahawa perbezaan ini tidak terlibat dengan satu sama lain ((Pekali Regresi 547.14 (95% CI: -54.83, 1149.10), nilai-p 0.073). Peristiwa titik akhir (kemasukan semula kerana masalah kegagalan fungsi jantung atau kematian) dalam masa sebulan dan dalam masa 6 bulan jangka masa discaj pesakit menunjukkan bahawa ia tidak berkaitan dengan sejauhmana perbezaan NT-proBNP. Walaubagaimanapun, analisis menunjukkan bahawa terdapat perkaitan di antara peristiwa jangka pendek dan pertengahan dengan tahap NT-proBNP pada masa discaj. Kebarangkalian kumulatif peristiwa titik akhir pesakit dengan tahap discaj NT-proBNP level < 727.5 pg/mL adalah kurang daripada mereka dengan ≥ 727.5 pg/mL dalam masa 6 bulan daripada waktu discaj (p-value 0.009). Perbezaan NT-proBNP tidak berkorelasi dengan kebanyakan perbezaan pembolehubah ekokardiografik dan elektrokardiografik.

Kesimpulan: Tahap perbezaan NT-proBNP dikaitkan dengan pengawalan kegagalan jantung dekompensasi akut. Simptom klinikal dan tanda-tandanya bukanlah merupakan petanda yang boleh dipercayai untuk penilaian kegagalan kawalan jantung, dan ianya tidak mencukupi dalam penilaian kemahuan untuk discaj. Terdapat peratus peristiwa titik akhir yang tinggi sejurus selepas discaj, dan ianya berkaitan dengan discaj EF dan NT-proBNP dan bukan perbezaan dalam hospital. Tiada korelasi signifikan di antara respon NT-proBNP dengan respon penemuan ekokardiografik atau pengukuran respon elektrokardiografik.

THE ROLE OF NT-PROBNP IN ASSESSING THE CONTROL OF DECOMPENSATED HEART FAILURE PATIENTS

ABSTRACT

Problem Statement: Several studies had emphasised the role of natriuretic peptides (BNP and NT-proBNP) to diagnose, to assess severity and prognosis, and to control heart failure in outpatient settings. However there were very few studies which showed its role in assessing the control of heart failure in hospitalised patients, and its impact on short and intermediate-term outcome.

Objective: To evaluate the role of NT-proBNP in assessing the control of decompensated heart failure patients, and its association to clinical features, outcome, echocardiographic findings, and electrocardiography.

Methods: Patients hospitalised with acute decompensated heart failure were enrolled in this prospective cohort study using systematic sampling. Thorough clinical assessment, with symptoms and signs scoring, NTproBNP, transthoracic echocardiogram and electrocardiography were performed at admission and discharge. Endpoint events (heart failure readmission or death) within one month and six months of patient's discharge were observed.

Results: Thirty patients hospitalised with acute decompensated heart failure were enrolled, with mean clinical score of 7.33 (1.47), median NT-proBNP (2470pg/L), and mean ejection fraction (EF) 38.48% (12.52) at admission. Mean admission period was 4.83 day (1.74). On discharge, the mean difference in clinical symptoms and

signs was 3.13 (95% CI 2.68-3.57), EF -5.75 (95% CI -8.95, -2.55) and median difference for NT-proBNP was 595 (p value < 0.001) had significantly improved. Despite that, the data analysis showed that these differences are not related to each others (Regression Coefficient 547.14 (95% CI: -54.83, 1149.10), p-value 0.073). Endpoint events (heart failure readmission or death) within one month and within 6 months of patient's discharge showed that they were not associated with the extent of NT-proBNP difference. However, analysis showed that there were association between both short-term and intermediate-term events with NT-proBNP level at discharge. Cumulative probability of endpoint events of patients with discharge NT-proBNP level < 727.5 pg/mL were less likely than those with ≥ 727.5 pg/mL within 6 months from discharge (p-value 0.009). NT-proBNP difference was not correlated with most of the echocardiographic and electrocardiographic variables differences.

Conclusion: NT-proBNP level difference was not associated with clinical symptoms and signs response of acute decompensated heart failure. Clinical symptoms and signs were not dependable marker for assessment of heart failure control, and were not sufficient in evaluation of discharge willingness. There was high percent of endpoint events following discharge, and these were related to EF and NT-proBNP discharge level rather than their in-hospital difference. There were no significant correlations between NT-proBNP difference with response of echocardiographic findings or response of electrocardiographic measurements.

1. CHAPTER 1 - INTRODUCTION

1.1. Introduction:

All over the world, Heart Failure is considered as a principal leading cause of death, hospitalisation, and rehospitalisation. Notwithstanding advances in the diagnosis and treatment of HF, including use of new investigations, devices, drugs, and heart transplantation, HF is still associated with considerable morbidity and mortality. Likely causes are inadequate drug optimisation HF medications and premature discharge of hospitalised patients with acute decompensation.

B-type natriuretic peptide (BNP) is a neurohormone secreted principally from the ventricles in response to intra-cardiac volume loading. BNP has the function of: (1) counter-regulation to angiotensin II, norepinephrine, and endothelin, (2) vasodilatation, and (3) diuresis. BNP is secreted from cleavage of its precursor (pro-BNP), which is stored in cardiomyocytes. Pro-BNP cleavage takes place by a protease enzyme, dividing into BNP and N-terminal pro-BNP (NT-proBNP). In relation to BNP, NT-proBNP has a longer sequence than BNP (76 vs 32 amino acids) and has a longer half-life (120 minutes vs 20 minutes). Both BNP and NTproBNP plasma concentration have been publicised to be useful in the diagnosis and prognosis of HF. In particular, lower plasma natriuretic peptides levels are predictive of a lower likelihood of adverse cardiac events. Thus, assessment of controlling acute decompensated HF by measurement of BNP plasma levels can be highly useful. The benefit behind is to use NT-proBNP to assess adequacy or optimisation of therapy to heart failure patients; and consequently decreasing rehospitalisation rates and decreasing the costs and expenditure of managing heart failure patients.

1.2. Heart Failure

1.2.1. Definition

Heart failure is the abnormality of heart structure or function causing failure of delivering oxygen at a rate proportionate with the needs of the organs' metabolism, with or without increased filling pressures (McMurray *et al.*, 2012). This leads to a group of clinical symptoms and signs that lead to recurrent hospitalisations, a poor quality of life, and a reduced life expectation (Mann, 2011). Thus, clinically we can define HF as a syndrome with typical symptoms (e.g. dyspnoea, ankle oedema, and easy fatigability) and signs (e.g. congested neck viens, rales, and displaced apex beat) caused by an abnormal cardiac structure or function.

Most of HF clinical symptoms are non-discriminating which makes them of limited diagnostic value (Mant *et al.*, 2009; Kelder *et al.*, 2011; Oudejans *et al.*, 2011). The clinical signs of HF, on the other hand, many of them result from salt and water retention and may resolve rapidly with diuretics and may not be present or easy missed in patients on such treatment. Therefore, underlying cause identification is fundamental to the diagnosis (as well as treatment) of HF(McMurray *et al.*, 2012).

1.2.1.1 Definition of the main terms used to describe HF

Left ventricular ejection fraction (LVEF or EF):

EF is the stroke volume (end-systolic volume subtracted from the end-diastolic volume) divided by the end-diastolic volume (Francis *et al.*, 2011; McMurray *et al.*, 2012). In systolic dysfunction, where LV contraction and emptying is reduced, stroke volume is preserved by an increase in end-diastolic volume through left ventricular dilation. This means that the heart "ejects a smaller fraction of a larger volume". The

worse the systolic dysfunction is, the more the EF is reduced. In general, this associated with greater end-diastolic and end-systolic volumes. The importance of EF is attained because its role outcome prediction (the poorer the EF the worse the outcome) and because its role in patients selection in clinical researches (Francis *et al.*, 2011; McMurray *et al.*, 2012).

Heart Failure with Reduced Ejection Fraction HF-REF "Systolic HF"

It is the form of HF in patients with LVEF of less than 50%, and mainly enrolled those with an EF ≤ 35%, when the classical features of systolic HF are present. Patients with an EF of 35–50% usually represent a 'grey zone' and they most likely have mild systolic failure (table 1.1)(McMurray *et al.*, 2012).

Table 1.1 Diagnosis of heart failure.[1]

The diagnosis of HF-REF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[2]
3. Reduced LVEF
The diagnosis of HF-PEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF[2]
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction

LA: left atrial; **LV:** left ventricular;

[1] "McMurray, J. J. V., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C. & Gomez-Sanchez, M. A. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal, 33(14), 1787-1847. Table 1"

[2] Signs may not be present in the early stages of HF (specially in HF-PEF) and in patients treated with diuretics

Heart Failure with Preserved Ejection Fraction HF-PEF "Diastolic HF"

It is the form of HF in patients with LVEF of more than 50%. Because diastolic LV dysfunction is not limited to HFPEF, but also can be detected in patients with HFREF, the term Diastolic HF was replaced by HFPEF (Borlaug and Paulus, 2011).

Diagnosis of HF-PEF is principally by exclusion of potential non-cardiac causes of the patient's complaints (e.g. anaemia, pulmonary illness). These patients typically do not have LV dilation, and they may have an increase in LV wall thickness and increased LA dimension. Echocardiographic evidence of diastolic dysfunction can be obvious in nearly everyone, which is accepted as the most probable cause of HF in these patients (Borlaug and Paulus, 2011; Francis *et al.*, 2011).

New York Heart Association (NYHA) Functional Classification

In this thesis we used the term HF for symptomatic syndrome, and it was graded according to the NYHA functional classification (Table 1.2). NYHA classification is providing us a simple method of classifying the extent and severity of heart failure; and it places patients in one of four classes based upon their symptoms and the limitation of physical activity. Despite the fact that there is an evident relationship between symptoms severity and patients' outcome, though symptom severity and left ventricular function are non-significantly correlated (McMurray, 2010; McMurray *et al.*, 2012).

Table 1.2: New York Heart Association (NYHA) Functional Classification.

Class	**Functional Capacity: How a patient with cardiac disease feels during physical activity**
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Adopted from American Heart Association website (Americal Heart Association).

Asymptomatic HF

Asymptomatic HF is the status of a patient who has never been presented with the typical clinical features of HF, despite of LV systolic dysfunction or other underlying structural abnormality (Francis *et al.*, 2011; McMurray *et al.*, 2012) .

Stable and decompensated HF

Stable treated HF patient is that patient with roughly unchanged symptoms and signs for at least a month. If stable HF worsens, the patient may have 'decompensated' HF, and when this happens suddenly, it's called 'acute decompensated HF', which usually leads to hospital admission, with substantial impact on survival (section 1.2.6; acute HF) (Francis *et al.*, 2011; McMurray *et al.*, 2012).

1.2.2. Epidemiology of Heart Failure

Unlike the adequate data for cardiovascular diseases and Percutaneous Coronary Intervention (PCI), which can be obtained from the reports of the National Cardiovascular Disease Database (NCVD), the actual figures of the heart failure epidemiology in Malaysia are largely absent. Only one hospital based study (Chong *et al.*, 2003) gave good idea about HF admissions in Malaysia. The ideal way of estimation of the ''true'' prevalence and incidence of HF ought to depend on surveys with randomly selected samples done in the community. This problem is not confined to Malaysia, but it can be seen in many places of the world, because of the natural history of the disease itself (Mosterd and Hoes, 2007). Study of Chong and his colleagues (2003) showed that 6.7% of all acute medical admissions to the Accident and Emergency Department over the 4-week study period were admitted with a primary diagnosis of either newly diagnosed (81%) or decompensated HF (19%). This may demonstrate the extent problem of HF in Malaysian hospitals.

In the western world, HF prevalence is assessed around 1–2%, and the incidence comes close to 5–10 per 1000 persons per year. Information about the occurrence of heart failure in the other parts of the world is largely deficient (Mosterd and Hoes, 2007).

Aetiology of HF is generally any disease process that breaks the heart pumping mechanism. The frequency of each disease involvement varies among epidemiological studies, based on the population considered and the method of ascertaining aetiology. In aforementioned hospital-based study held in Malaysia, coronary artery disease was the principal cause of CHF, accounting for 49.5% of patients from all ethnic groups. This was followed by hypertension, which accounted for 18.6% of cases (Chong *et al.*, 2003). The figures were not much different from population-based study held in South London, UK. The percentage of heart failure with ischaemic heart disease allocated as the aetiology was 51% (Fox *et al.*, 2001) (Fig. 1.1).

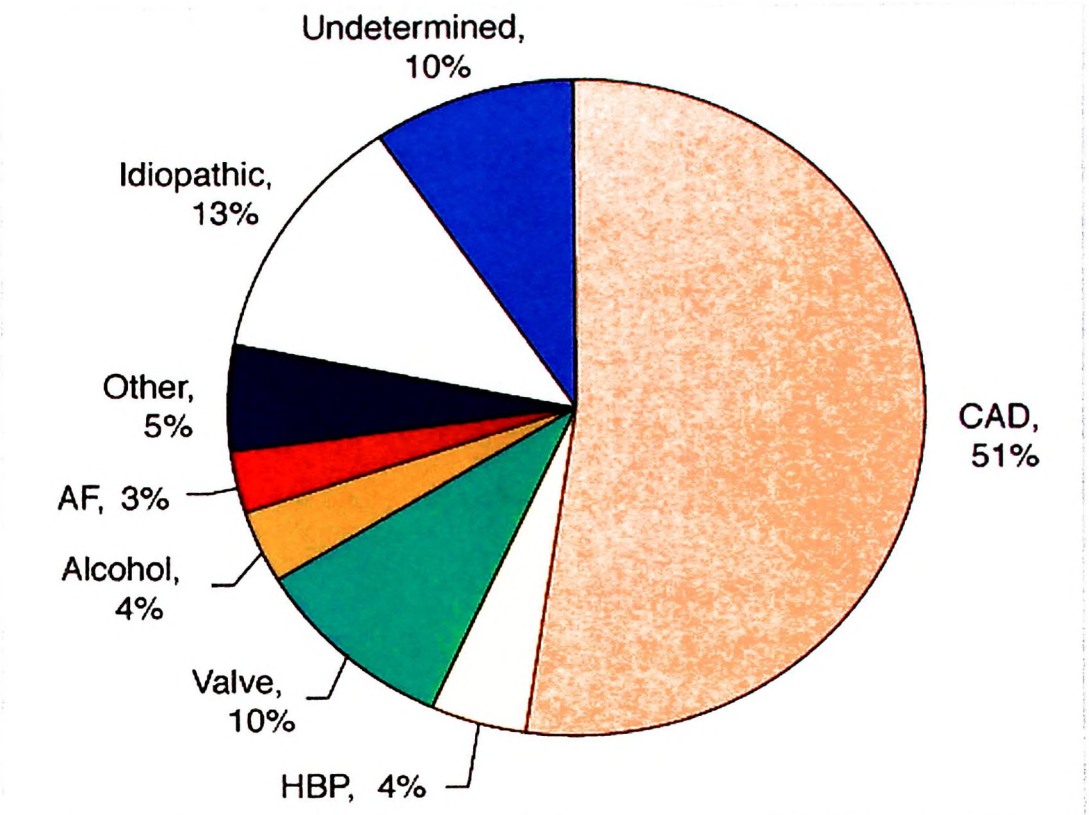

Fig 1.1: **Aetiology of heart failure in a study of incident (new) cases in Bromley, South London, for cases younger than 75 years of age, based on full investigation including nuclear scintigraphy and cardiac catheterisation. AF, atrial fibrillation; CAD, coronary artery disease; HBP, high blood pressure. Adopted from "Dar, O. & Cowie, M. R. (2011). The Epidemiology and Diagnosis of Heart Failure. In: Fuster, V., Walsh, R. A. and Harrington, R. A. (eds.), Hurst's the heart 13th ed., Vol. 1. New York: McGraw-Hill. Figure 27-2. (Dar and Cowie, 2011)**

The epidemiological and aetiological profile for HF-PEF seems to be different from that of HF-REF (Lam *et al.*, 2011). Those with HF-PEF are usually older and more frequently obese and female than those with HF-REF. Patients with HF-PEF are less probably have coronary heart disease and are more prone to have hypertension and atrial fibrillation (AF). They have generally a better outcome than those with HF-REF (Lam *et al.*, 2011; Rusinaru *et al.*, 2012).

1.2.3. Pathophysiology of Heart Failure:

1.2.3.1 Pathophysiologic Concepts of Heart Failure

The pathophysiology of HF is a complex subject, and it is still not fully understood. Even though the HF treatment has progressed well over the last years, but it is not curative yet. A better perception of the HF pathophysiology can allow us to identify early biomarkers of early heart failure or even pre–heart failure, consequently permitting strategy of aggressive and cost-effective prevention, before the patient's condition reaches the late stages of the syndrome.

HF, as mentioned, is caused by any structural or functional abnormalities of the heart, and subsequently both structural and functional changes will be involved. The event can be evident clinically, such as acute infarction or it may be insidious and slowly progressive, such as genetic mutations. The cardiac myocytes responds to LV damage with chronic hypertrophic and fibrotic adaptation. As a result, LV may dilate, thereby temporarily maintaining stroke volume and the LV performance can be maintained despite of a low stroke volume to achieve metabolic needs. Symptoms thereby can be only minimal. Eventually though, with progressive LV enlargement, the heart capability to eject blood is impaired along with rise in LV filling pressure, leading to breathlessness, decreased effort tolerance and peripheral congestion. In the late stages, further dilation of the left ventricular and atrial chambers leads to mitral regurgitation and distortion of normal architecture, with elongated myocytes and extensive fibrosis. As a conclusion, the consequences are decreased filling, impaired emptying, and cardiac dysrhythmias. (Francis *et al.*, 2011)

1.2.3.2 Aetiology and mechanisms of Heart Failure

Since the fact that any form of heart disease can induce heart failure, there is no single mechanism that explains the malfunction of heart muscle, at both organ and cellular levels. The aetiology can be classified in 6 categories:

1. Failure due to malfunctioned myocardium
    - Myocardial cell loss (e.g. MI)
    - Uncoordinated myocardial contraction (e.g. LBBB, RV pacing)
    - Impaired contractile force (e.g. cardiomyopathy or cardiotoxicity)
    - Disorientation of cells (eg, hypertrophic cardiomyopathy)
2. Failure primarily related to external work overload (e.g. hypertension or aortic valve stenosis).
3. Failure related to valvular defects
4. Failure result from cardiac arrhythmia (e.g. incessant tachycardia)
5. Failure caused by pericardial diseases (e.g. tamponade)
6. Congenital anomalies of the heart. (Francis *et al.*, 2011)

In diverse circumstances and at multiple points of time, various subsequent physiological changes play role in the heart failure syndrome (Table 1.3). One of the good examples is, when the myocardium fails, LV dilatation can take place, preserving the stroke volume (Starling effect). This dilatation may result in functional mitral regurgitation, that provokes a secondary volume overload for the already weakened LV. Adaptive or compensatory processes in the periphery happen and can affect in adverse manner the heart, kidneys, muscles, endothelium, peripheral vasculature, and multiple reflex control mechanisms, putting in more to the complexity of the HF syndrome (Table 1.4). Eventually, differentiating primary aetiological forces from secondary phenomena is difficult. (Francis *et al.*, 2011)

Table 1.3 Possible Mechanisms of Myocardial Failure

- Loss of myocytes
- Hypertrophy of remaining myocytes
- Energy production and utilisation
    - Oxygen and energy supply
    - Substrate utilisation and energy storage
    - Inadequate mitochondria mass and function
- Ventricular remodeling
- Contractile proteins
    - Abnormal myofibrillar or myosin ATPase
    - Abnormal myocardial proteins
    - Defective protein synthesis
    - Nonuniformity of contraction and function
- Activation of contractile elements
    - Membrane Na^+, K^+-ATPase defects
    - Abnormal sarcoplasmic reticulum function (Abnormal Ca^{2+} release, Abnormal Ca^{2+} uptake)
- Abnormal myocardial receptor function
    - Down-regulation of β adrenoreceptors
    - Decreased β_1 receptors
    - Decreased Gs protein
    - Increased G1 protein
- Autonomic nervous system
    - Abnormal myocardial norepinephrine function or kinetics
    - Abnormal baroreceptor function
- Increased myocardial fibroblast growth and collagen synthesis
- Aging changes, presbycardia
- Sustained tachycardia
- Miscellaneous

ATPase: adenosine triphosphate; Ca^{2+}: calcium;
Na^+,K^+-ATPase, sodium-potassium adenosine triphosphate.

Adopted from "Francis, G., Sonnenblick, E., Tang, W. & Poole-Wilson, P. (2011). Pathophysiology of Heart Failure. In: Fuster, V., Walsh, R. A. and Harrington, R. A. (eds.), Hurst's the heart 13th ed., Vol. 1. New York: McGraw-Hill. Table 26.3(Francis *et al.*, 2011)

Table 1.4 Compensatory Mechanisms in Heart Failure

Autonomic nervous system
Heart Increased heart rate Increased myocardial contractile stimulation Increased rate of relaxation
Peripheral circulation
Arterial vasoconstriction (increased afterload) Venous vasoconstriction (increased preload)
Kidney (renin–angiotensin–aldosterone system)
Arterial vasoconstriction (increased afterload) Venous vasoconstriction (increased preload) Sodium and water retention (increased preload and afterload) Increased myocardial contractile stimulation
Endothelin-1 (increased preload and afterload)
Arginine vasopressin (increased preload and afterload)
Atrial and brain natriuretic peptides (decreased afterload)
Prostaglandins
Peptides
Frank-Starling law of the heart
Increased end-diastolic fiber length, volume, and pressure (increased preload)
Hypertrophy
Stem cell maturation replacing lost myocardium
Peripheral oxygen delivery
Redistribution of cardiac output Altered oxygen-hemoglobin dissociation Increased oxygen extraction by tissues
Anaerobic metabolism

Adopted from "Francis, G., Sonnenblick, E., Tang, W. & Poole-Wilson, P. (2011). Pathophysiology of Heart Failure. In: Fuster, V., Walsh, R. A. and Harrington, R. A. (eds.), Hurst's the heart 13th ed., Vol. 1. New York: McGraw-Hill. Table 26.4(Francis *et al.*, 2011)

There is no agreed or satisfactory classification for the causes of HF, because of overlap between groups. However, the latest ESC guideline demonstrates clear and clinically oriented aetiological classification. The details are listed in table 1.5.

Table 1.5 Aetiology of heart failure

Myocardial disease
1. Coronary artery disease 2. Hypertension [a] 3. Cardiomyopathy [b] a. Familial i. Hypertrophic ii. Dilated iii. Arrhythmogenic right ventricular cardiomyopathy iv. Restrictive v. Left ventricular non-compaction b. Acquired i. Myocarditis (inflammatory cardiomyopathy) Infective • Bacterial • Spirochaetal • Fungal • Protozoal • Parasitic • Rickettsial • Viral Immune-mediated • Tetanus toxoid, vaccines, serum sickness • Drugs • Lymphocytic/giant cell myocarditis • Sarcoidosis • Autoimmune • Eosinophilic (Churg–Strauss) Toxic • Drugs (e.g. chemotherapy, cocaine) • Alcohol • Heavy metals (copper, iron, lead) ii. Endocrine/nutritional • Phaeochromocytoma • Vitamin deficiency (e.g. thiamine) • Selenium deficiency • Hypophosphataemia • Hypocalcaemia iii. Pregnancy iv. Infiltration • Amyloidosis • Malignancy
Valvular heart disease
Mitral Aortic Tricuspid Pulmonary
Pericardial disease
Constrictive pericarditis Pericardial effusion
Endocardial disease
• Endomyocardial diseases with hypereosinophilia [hypereosinophilic syndromes (HES)] • Endomyocardial disease without hypereosinophilia [e.g. endomyocardial fibrosis (EMF)] • Endocardial fibroelastosis
Congenital heart disease
Arrhythmia
Tachyarrhythmia

Atrial Ventricular Bradyarrhythymia Sinus node dysfunction Conduction disorders
High output states
Anaemia Sepsis Thyrotoxicosis Paget's disease Arteriovenous fistula
Volume overload
Renal failure Iatrogenic (e.g. post-operative fluid infusion)

a Both peripheral arterial and myocardial factors contribute to the development of heart failure.
b Other inherited diseases may have cardiac effects. e.g. Fabry disease.

Adopted from "McMurray, J. J. V., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C. & Gomez-Sanchez, M. A. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal, 33(14), 1787-1847. Table 3"

1.2.3.3 Heart Failure with Reduced or Preserved Ejection Fraction

The fundamental characteristic of HFREF is a dilated LV and impaired ejection fraction. The left ventricular remodelling or dilation may need years to take place. Frequently, the process can be attenuated, eliminated, or even reversed with appropriate medical management (McMurray, 2010; McMurray *et.al.*, 2012).

Heart failure with a preserved ejection fraction (HFPEF), or diastolic heart failure, often takes place together with systolic heart failure. Nevertheless, certain elements of HFPEF are distinct including reduced LV filling, increased chamber stiffness, and increased LV end-diastolic pressure relatively to end-diastolic volume. The left ventricular diameter is often normal with myocardial hypertrophy being common but not consistent (Borlaug and Paulus, 2011).

Stages of Diastolic dysfunction:

It is clinically useful to consider diastolic dysfunction as a range or a band of disease that progresses from mild to more advanced stages, and ultimately develops into and irreversible. However, not all patients progress linearly along the pathway and reversal of the path is possible (Armstrong and Ryan, 2009; DeMaria and Blanchard, 2011). These stages or grades, together with the pathophysiologic changes that characterise each, are outlined in Table 1.6 and demonstrated in Fig 1.2.

Table 1.6: Stages of Diastolic Dysfunction

Grade	Stage	Dominant Pathophysiology
1	Impaired relaxation	Delayed LV early diastolic active relaxation Normal LA pressure Low opening LA-LV pressure gradient Reduced LV suction force
2	Pseudo-normalisation	Delayed LV early diastolic active relaxation Mildly elevated LA pressure Low opening LA-LV pressure gradient Reduced LV suction force
3	Restrictive filling (reversible)	Noncompliant LV chamber (increased stiffness) Diminished LV suction forces High opening LA-LV pressure gradient Elevated LA pressure (inflow by "pushing" blood) Failing LA contractility Responds positively to preload reduction
4	Restrictive filling (irreversible)	Noncompliant LV chamber (increased stiffness) Diminished LV suction forces High opening LA-LV pressure gradient Elevated LA pressure (inflow by "pushing" blood) Failing LA contractility No improvement preload reduction

Adopted from: "Armstrong, W. F. & Ryan, T. (2009). Feigenbaum's echocardiography. 7th ed. Philadelphia: Lippincott Williams & Wilkins. Table 7.1"

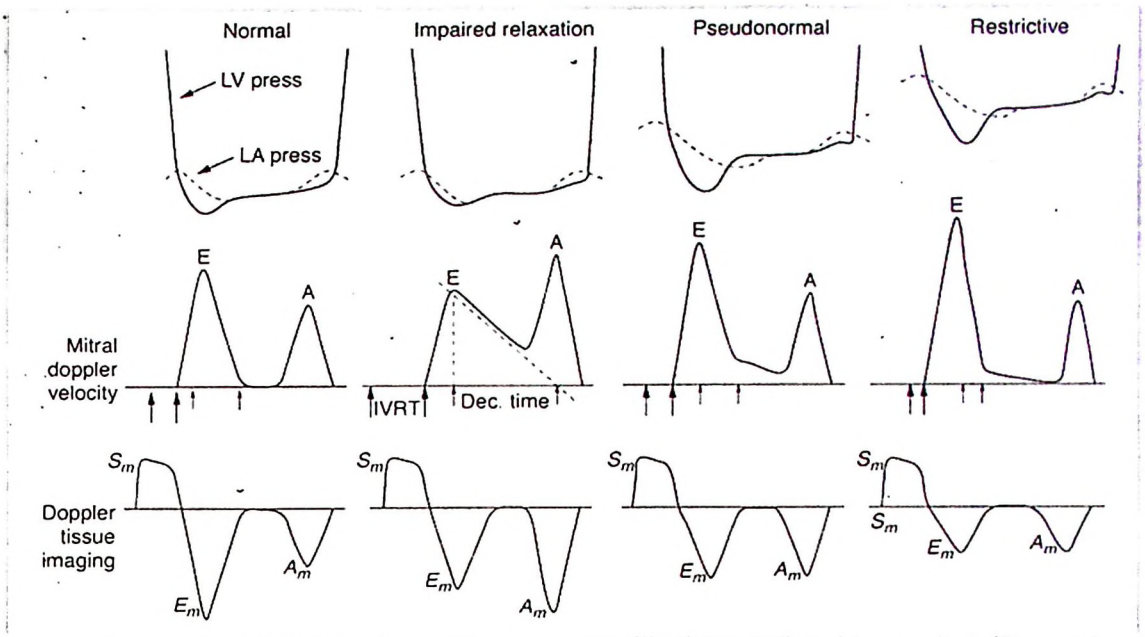

Fig 1.2: Doppler assessment of progressive diastolic dysfunction utilising transmitral pulsed-wave Doppler and mitral annular tissue Doppler imaging.

A, atrial component of LV filling;
Am, myocardial velocity during filling produced by atrial contraction;
Dec. Time, E wave deceleration time;
E, early LV filling velocity; Em, early diastolic myocardial velocity;
IVRT, isovolumic relaxation time; Sm, systolic myocardial velocity.
Adopted from: "DeMaria, A. N. & Blanchard, D. G. (2011). Echocardiography. In: Fuster, V., Walsh, R. A. and Harrington, R. A. (eds.), Hurst's the heart 13th ed., Vol. 1. New York: McGraw-Hill."

1.2.3.4 Neurohormonal Changes in Heart Failure

Neuro-hormonal activation is a feature of HF, seemingly in attempt to maintain perfusion pressure. A significant number of neuro-hormones have been found to circulate in abnormal quantities in heart failure (Table 1.7). The natriuretic peptides, particularly, atrial and B-type natriuretic peptides (ANP and BNP), are considered counter-regulatory hormones, hence they tend to reduce right atrial pressure, systemic vascular resistance, aldosterone secretion, sympathetic nerve stimulation, and hypertrophy of cells and can enhance sodium excretion. The predominant consequence of most neuro-hormone release in HF is vasoconstriction coupled with salt and water retention. Eventually, excessive chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) aids in LV

remodelling at the cellular level, and consequently helps in the disease progression. Other hormones, neuro-hormones, and cytokines (detailed in Table 1.7) also participate in the heart failure pathophysiological changes, promoting fibrosis, hypertrophy, and further impairing LV function. In addition, specific molecular abnormalities can be identified in the myocytes of the failing heart.

Table 1.7 Neurohormonal Changes in Heart Failure [a]

Increased sympathetic-nervous system activity (increased norepinephrine, epinephrine)
Increased endothelin
Increased arginine vasopressin
Increased renin and angiotensin II
Increased aldosterone
Increased neuropeptide Y
Increased atrial and B-type natriuretic peptides
Increased
Insulin Cortisol Growth hormone (decreased insulinlike growth factor 1) Tumor necrosis factor Interleukin-6 Vasoactive intestinal peptide Adrenomedullin Urodilantin Urotensin-II Cardiotrophin-I
Increased dopamine
Increased prostaglandins (PGI2, PGE2)
Increased vasodilator peptides (eg, bradykinin)

a Measurements in individual patients vary significantly, and changes may not always be present.
PGE2: prostaglandin E2; **PGI2**: prostaglandin I2.
Adopted from "Francis, G., Sonnenblick, E., Tang, W. & Poole-Wilson, P. (2011). Pathophysiology of Heart Failure. In: Fuster, V., Walsh, R. A. and Harrington, R. A. (eds.), Hurst's the heart 13th ed., Vol. 1. New York: McGraw-Hill. Table 26.5 (Francis *et al.*, 2011)

1.2.4. Diagnosis of Heart Failure

The diagnosis of HF can be hard and complicated, especially in the syndrome early stages. The most recent guidelines from the European Society of Cardiology (ESC) on the diagnosis and treatment of acute and chronic heart failure recommends that

symptoms should be existent, with objective evidence of HF provided preferably by echocardiography. Where an element of uncertainty persists, response to therapy directed toward heart failure can help confirm or refute the diagnosis (McMurray *et al.*, 2012). The Heart Failure Society of America guidelines suggest a similar approach, with a careful history enhanced by clinical examination and investigations to evaluate cardiac structure and function (Lindenfeld *et al.*, 2010). In both guidelines, the estimation of the concentration of plasma B-type natriuretic peptide is advocated to assist in making or ruling out a diagnosis of HF in doubtful situations.

1.2.4.1 Symptoms and signs

Numerous symptoms of HF are non-specific and do not assist much in HF discrimination from other problems. More specific symptoms (i.e. orthopnoea and paroxysmal nocturnal dyspnoea) are less common, especially in patients with milder symptoms; therefore, they are insensitive (Mant *et al.*, 2009; Kelder *et al.*, 2011; Oudejans *et al.*, 2011). Several signs of HF are caused by salt and water retention, and are, therefore, also not specific. Peripheral oedema has other causes as well. In addition, these signs resolve quickly with diuretics and may be absent in patients receiving such therapy. More specific signs, such as prominent jugular venous pulsation and displaced apical impulse, are harder to distinguish and, consequently, the agreement between different doctors examining the same patient may be poor (Mant *et al.*, 2009; Kelder *et al.*, 2011; Oudejans *et al.*, 2011). Hence, these facts necessitate the need to achieve objective evidence of a structural or functional cardiac abnormality that could be blamed for patient's symptoms and signs, and to secure the diagnosis of HF. However, the clinical features are of great importance in monitoring patient's response to management, over time stability, and outcome (McMurray *et al.*, 2012).

Table 1.8: Symptoms and signs of heart failure

Symptoms	Signs
Typical	**More specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover after exercise	Cardiac murmur
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Peripheral oedema (ankle, sacral,scrotal)
Wheezing	Pulmonary crepitations
Weight gain (>2 kg/week)	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Weight loss (in advanced heart failure)	Tachycardia
Bloated feeling	Irregular pulse
Loss of appetite	Tachypnoea (>16 breaths/min)
Confusion (especially in the elderly)	Hepatomegaly
Depression	Ascites
Palpitations	Tissue wasting (cachexia)
Syncope	

Adopted from "McMurray, J. J. V., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C. & Gomez-Sanchez, M. A. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal, 33(14), 1787-1847. Table 4"

1.2.4.2 Essential initial investigations:

The following investigations may be used to confirm or refute the diagnosis of HF:

Chest Radiograph

The main benefit of a chest X-ray is to rule out other causes for breathlessness, such as pleural effusion, pneumothorax, lung cancer, or pneumonia. If pulmonary oedema is found, this supports a diagnosis of heart failure. Cardiothoracic ratio is of moderate value in diagnosing HF as a cause of dyspnoea. Echocardiography has substituted chest X-ray in determination of cardiac chamber dimensions (Dar and Cowie, 2011).

Electrocardiogram

Clinically, the ECG can provide evidence to detect arrhythmia, suggestive of previous ischaemia, or ventricular hypertrophy. Clinical studies showed that a entirely normal ECG is unlikely in a patient with heart failure, however, its positive predictive value is also low in the old-age where ECG abnormality is commonly seen (Zaphiriou *et al.*, 2005).

Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) are produced by the cardiomyocytes, and its plasma level is elevated in left ventricular abnormalities (LVH, systolic or diastolic LV dysfunction, and principally in those with overt heart failure) (Balion *et al.*, 2008b; Dar and Cowie, 2011; Francis *et al.*, 2011). BNP value as a rule-out test for heart failure in patients presenting with new symptoms, in either primary or secondary care settings, is now very well known (Balion *et al.*, 2008b; Boldanova *et al.*, 2010; Chiong *et al.*, 2010; Dar and Cowie, 2011; McMurray *et al.*, 2012). Other conditions, like acute myocardial infarction, pulmonary embolism, and renal failure, can be associated with elevation in plasma

concentration of BNP; besides the normal values are higher in the elderly and women (Bruins *et al.*, 2004; Galasko *et al.*, 2005; Balion *et al.*, 2008b). The current European and American guidelines for heart failure recommend that the measurement of the plasma concentration of natriuretic peptides (BNP or NT-proBNP) can be useful in confirming or excluding the diagnosis of heart failure, specially at the time of first presentation or in the acute setting (Lindenfeld *et al.*, 2010; McMurray *et al.*, 2012). A recent meta-analysis of diagnostic studies established the usefulness of plasma BNP concentration in the management approach of patients with suspected heart failure, with diagnostic value greater than the ECG (Mant *et al.*, 2009).

Echocardiography

Trans-thoracic echocardiography (TTE) is a quite simple and effective technique used in evaluation of cardiac structure and function. So far, it is considered as the main imaging method used in cardiology. Normality can be difficult to interpret, particularly for those with poor images because of thick chest wall, obesity, or chronic airway disease; however, satisfactory imaging could be obtained in up to 90% of free-living subjects (Dar and Cowie, 2011; McMurray *et al.*, 2012). The problem with echocardiography is its limited availability, particularly in the general practice settings.

Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) imaging provides high-quality images for both cardiac structure and function. Besides that, contrast imaging, with agents such as gadolinium, can demonstrate features of inflammation, fibrosis, and information on myocardial perfusion. Although with less reliability, valve function can also be

assessed. The expense of the equipment and its lack of availability and portability make magnetic resonance imaging of limited use particularly in acute settings and population-based studies(Dar and Cowie, 2011; McMurray *et al.*, 2012). Based on the current European guidelines, CMR imaging is only recommended to assess cardiac structure and function especially in subjects with inadequate echocardiographic images obtained or where the echocardiographic findings are inconclusive (McMurray *et al.*, 2012).

Cardiac Catheterisation

In heart failure, coronary angiography is indicated in patients with angina pectoris, who are believed fit for coronary revascularisation, or to evaluate the coronary anatomy(McMurray *et al.*, 2012). Yet, cardiac catheterisation is not limited to coronary angiography. It may also enable us to know the measurement of intracardiac pressures, to estimate cardiac output, to detect valvular abnormalities, to quantify LVEF, to assess diastolic function, and to detect coronary artery disease (Dar and Cowie, 2011). Each of these modalities could be considered according to the patient's presentation or needs.

Other investigations

Special investigations might be considered in selected patients, based on their clinical presentation.

- Exercise Stress Test
- Stress Echocardiography
- Trans-oesophageal echocardiography (TOE)
- Ambulatory electrocardiographic monitoring
- Cardiac computed tomography and Multi-detector CT (MDCT)

- Single photon emission computed tomography (SPECT)
- Positron emission tomography (PET)]
- Endomyocardial biopsy
- Genetic testing

1.2.4.3 Algorithm for the diagnosis of heart failure

Fig 1.3 demonstrates the ESC 2012 recommended approach in patients presenting to hospital with suspected HF(McMurray *et al.*, 2012). This approach is not much different from algorithm designed in the Malaysian Clinical Practice Guidelines (CPG) for heart failure (Rajadurai *et al.*, 2007).

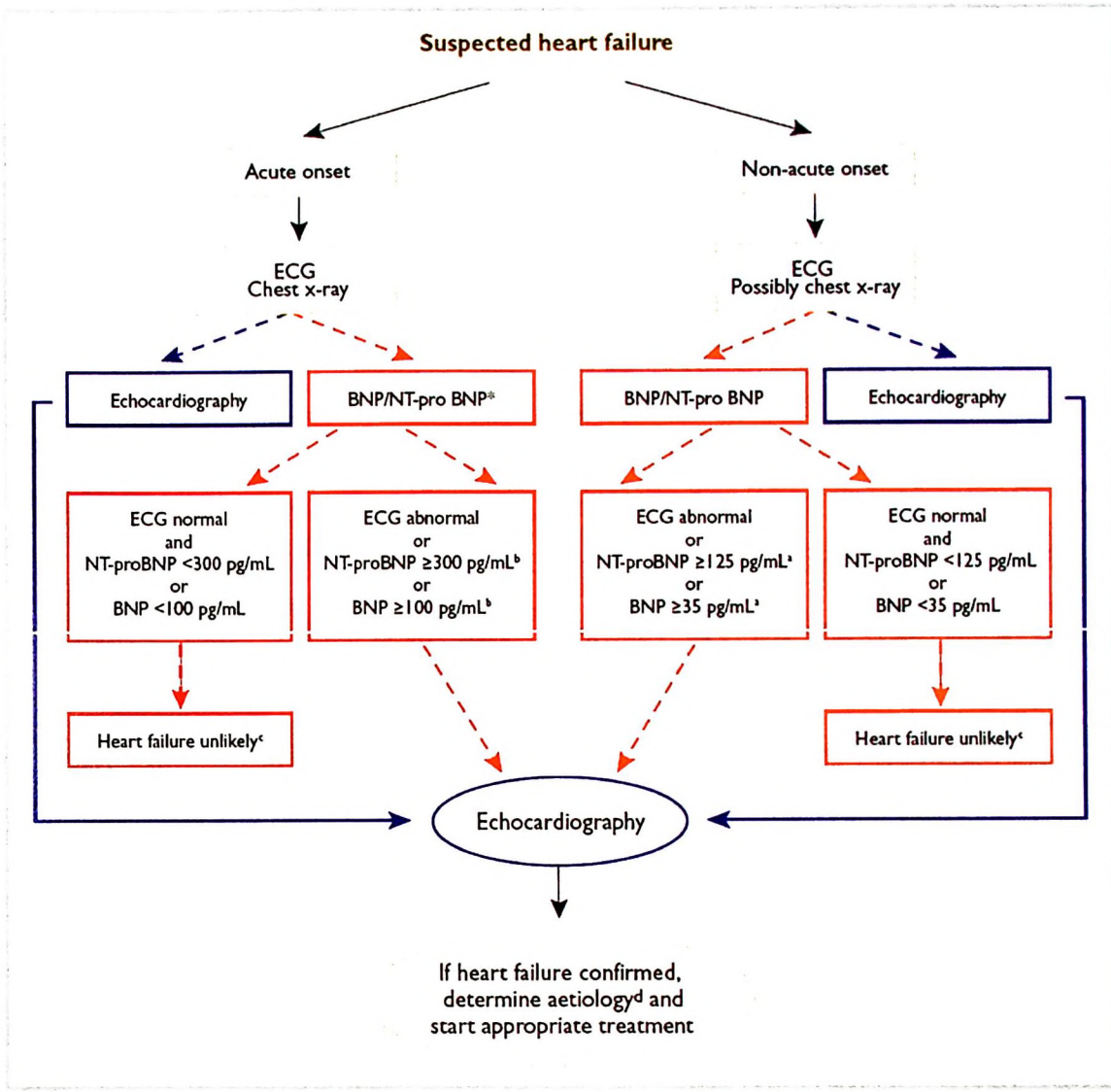

Figure 1.3: Diagnostic flowchart for patients with suspected heart failure, showing alternative 'echocardiography first' (blue) or 'natriuretic peptide first' (red) approaches.

[a] Exclusion cut-off points for natriuretic peptides are chosen to minimise the false-negative rate while reducing unnecessary referrals for echocardiography.

[b] Other causes of elevated natriuretic peptide levels in the acute setting are an acute coronary syndrome, atrial or ventricular arrhythmias, pulmonary embolism, and severe chronic obstructive pulmonary disease with elevated right heart pressures, renal failure, and sepsis. Other causes of an elevated natriuretic level in the non-acute setting are: old age (>75 years), atrial arrhythmias, left ventricular hypertrophy, chronic obstructive pulmonary disease, and chronic kidney disease.

[c] Treatment may reduce natriuretic peptide concentration, and natriuretic peptide concentrations may not be markedly elevated in patients with HF-PEF.

Adopted from "McMurray, J. J. V., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C. & Gomez-Sanchez, M. A. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal, 33(14), 1787-1847. Fig 1"