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The struggle towards a Universal Definition of Heart Failure—how to proceed?

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Abstract

We propose a Universal Definition of Heart Failure based on the pathophysiological concept of “cardiac dysfunction with congestion”; congestion being defined as high atrial and venous pressures. In clinical practice, increased plasma concentrations of natriuretic peptides and atrial dilation are the hallmarks of congestion.

Currently, the diagnosis of heart failure is based on symptoms and signs that are neither sensitive nor specific and often ignored until severe enough to precipitate hospitalisation. Cardiac dysfunction and congestion commonly exist and progress for years before the onset of symptoms. The consequences of delayed diagnosis may be severe. Objective and verifiable diagnostic criteria for heart failure are desirable for many reasons, but particularly to improve patient management and outcomes and scientific communication. Enabling early diagnosis encourages timely intervention to slow, halt or reverse disease progression.

Myocardial secretion of natriuretic peptides is a key physiological defence against congestion; only when this defence is overwhelmed will congestion become clinically overt. Accordingly, increased plasma concentrations of natriuretic peptides due to cardiac dysfunction, rather than symptoms, should be prerequisite for the diagnosis of heart failure. Atrial dilation confirms a cardiac cause for the increase in natriuretic peptides.

This definition of heart failure would bring it into line with those for other common medical conditions such as myocardial infarction, diabetes and hypertension, that are based on a combination of pathophysiological concepts supported by objective measurements rather than delaying diagnosis until the onset of symptoms. This new definition will have profound effects on the prevalence and management of heart failure.

Introduction

Recently, the 4th Universal Definition of Myocardial Infarction was published (1). Perhaps it is time to consider a First Universal Definition of Heart Failure. Objective, clinically-verifiable, diagnostic criteria are not only desirable for the scientific classification of disease but also for describing its epidemiology, for informing patients on the nature and prognosis of their disease, for choosing and implementing treatment in a timely fashion, for strategic planning of clinical services and for selection and risk stratification of those invited to participate in research (2, 3). Diagnostic uncertainty has far-reaching consequences but insisting on diagnostic certainty may also be detrimental if it delays intervention until the disease is severe, or inappropriately excludes patients from treatment, or underestimates the size of the problem. Diagnostic criteria that are sensitive might lack specificity, but this can be resolved by further investigation, creating the opportunity for an early, accurate diagnosis and timely intervention.

Currently, the diagnosis of heart failure is based mainly on subjective criteria and mostly made by clinicians who have little training in cardiology and even less in heart failure. Those that are trained have widely varying experience, opinions, motivations and access to diagnostic investigations. Currently, for many patients, a diagnosis is made only when symptoms and signs are severe enough to require hospitalisation (4-7). However, cardiac dysfunction often exists and progresses for years before a final insult causes the onset, often sudden and catastrophic, of symptoms and signs of heart failure. Many people have exertional breathlessness long before they receive a diagnosis of heart failure, which they attribute to being old or unfit, and manage by adopting a sedentary lifestyle. Waiting for diagnostic certainty, only once symptoms and signs are obvious, may miss the best opportunity to modify the natural history of heart failure.

Guidelines define heart failure as the presence of typical symptoms and signs due to cardiac dysfunction (8). However, there are many causes of fatigue, breathlessness and ankle swelling; symptoms and signs are neither sensitive nor specific for heart failure. Guidelines indicate that low plasma concentrations of B-type natriuretic peptide (BNP), or an N-terminal fragment of the pro-peptide (NT-proBNP), rule out a diagnosis of heart failure, but the perception that there are many reasons for a high BNP/NT-proBNP has led to recommendations that they should not be used to confirm (“rule-in”) the diagnosis (8). However, the problem may lie not with BNP/NT-proBNP but rather with the clinical and imaging “gold-standards” against which they are compared and a clinical convention focussed on identifying, symptomatic, late-stage disease rather than early detection and treatment to slow or prevent its evolution. Perhaps natriuretic peptides should be the gold-standard against which other criteria are tested? Then there would be no such thing as a “false-positive” test. There are many parallels between this situation and those that led to the adoption of high sensitivity troponin in the Universal Definition of Myocardial Infarction.

For other medical conditions that have many different causes, such as diabetes and hypertension, diagnosis is based on a combination of pathophysiological concepts and objective measurements (such as blood pressure or glucose), with a threshold above which morbidity and mortality are predicted to increase and that might be modified by interventions. Should the strategy be any different for heart failure? Pathophysiologically, heart failure can be defined as cardiac dysfunction associated with renal retention of water and salt, causing a rise in atrial and venous pressure and volume (ie:- engorgement or ‘circulatory’ congestion) followed by an increase in water and salt in tissues (oedema or “tissue” congestion) (Figure 1) or, more simply, as cardiac dysfunction with congestion (Table 1; Figure 2). All patients with heart failure ultimately have a cardio-renal syndrome. Congestion can also be due to renal disease with little evidence of cardiac dysfunction. Measurement of serum creatinine

will determine where the patient lies on this cardio-renal spectrum of congestion and whether they should receive a diuretic or dialysis. Congestion causes symptoms when severe and is associated with a poor prognosis (9-13); relief of congestion, whether by diuresis or dialysis, improves symptoms and outcomes (14, 15). Although evidence is lacking that conventional diuretic agents, such as furosemide, improve prognosis, they certainly often do. Within days of stopping diuretic treatment, congestion often worsens, symptoms often deteriorate and many patients would die in pulmonary oedema if left untreated (16).

What then might be an early and objective marker of congestion? Increased myocardial secretion of natriuretic peptides, which promote sodium and water excretion, is a key physiological defence against congestion; only when this defence is overwhelmed does congestion become clinically overt. Accordingly, increased plasma concentrations of BNP/NT-proBNP due to cardiac dysfunction could be considered diagnostic of heart failure, even in the absence of symptoms. Patients with cardiac dysfunction on imaging and a normal plasma BNP/NT-proBNP generally do not have congestion and have a good prognosis (15). Those with raised plasma concentrations of BNP/NT-proBNP have an adverse prognosis regardless of the reason for cardiac dysfunction, unless it can be fixed (17). Persistent reduction in plasma BNP/NT-proBNP amongst patients with heart failure is associated with myocardial remodelling and a favourable outcome (14, 15)(18)(19)(20).

Natriuretic peptides are robust biomarkers of congestion but do not pinpoint its cause. Having established that congestion is present, a clinical history, blood tests and imaging are required to determine the presence and nature of cardiac dysfunction or other causes of congestion such as renal disease and hypo-albuminaemia. There are some circumstances where plasma BNP/NT-proBNP might be misleadingly low, including obesity (21, 22), treatment with diuretics (16) and, more rarely, constrictive pericarditis. Imaging the atria and great veins, measurements of vascular or intra-cardiac pressures, assessment of lung congestion and a

variety of bio-impedance devices are other ways to assess congestion but may be less widely available, more expensive and have a less robust evidence-base than do natriuretic peptides (9, 10, 12, 13, 16, 23). However, if necessary, these technologies can be used to confirm that congestion exists and to identify its cause, severity and distribution.

An inverse relationship between body mass index (BMI) and plasma concentrations of natriuretic peptides exists both before and after heart failure has developed (24-27). Obesity is common amongst patients with heart failure (28), especially those with a normal LVEF (HFpEF). Consequently, even when atrial pressures and volumes are increased, obese patients may not always have an elevated BNP/NT-proBNP by current criteria (29). This might be explained by greater pericardial restraint due to an increase in epicardial adipose tissue causing a reduction in transmural atrial pressure, a major stimulus to myocardial secretion of natriuretic peptides (29). Packer has suggested further sub-types of HFpEF, including a group with severe obesity, increased plasma volume and a low or normal plasma BNP/NT-proBNP (22), although in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial), patients who had higher plasma volumes also had higher plasma NT-proBNP (30). Most patients with heart failure will have an elevated BNP/NT-proBNP even if they have severe obesity. In a meta-analysis predominantly comprising HFpEF, the median NT-proBNP was 357 (144-938)ng/L for those with a BMI $>40\text{kg/m}^2$ (21). For patients with HFpEF and a BMI $>35\text{kg/m}^2$ in the I-PRESERVE (Irbesartan in HF and PRESERVED Ejection fraction) trial median NT-proBNP was 254ng/L (31) and for those $>40\text{kg/m}^2$ enrolled in TOPCAT the average was 1,853ng/L (27). Overall, these observations suggest that BNP/NT-proBNP retains diagnostic value in severe obesity, although thresholds should be adjusted (21), and highlight the need for further research into the relationship between obesity and heart failure (32-35).

Although plasma concentrations of natriuretic peptides are, on average, lower in obese people, they still indicate a greater future risk of developing clinically overt heart failure (24, 36). Natriuretic peptides are also powerful prognostic markers for patients with heart failure and a reduced left ventricular ejection fraction (HFrEF) or HFpEF, even after adjusting for BMI (26, 27, 37). There is a U-shaped relationship between BMI and prognosis with risk reaching a nadir for both HFrEF and HFpEF at a BMI of 33kg/m^2 , with risk being similar at values of 25kg/m^2 and 40kg/m^2 (28). Therefore, obese patients may have lower plasma concentrations of natriuretic peptides but they also have a better prognosis unless obesity is severe; in other words, natriuretic peptides track with prognosis rather than haemodynamics. Whether the “obesity paradox” reflects reverse-causality, or whether a higher BMI confers protection is uncertain (38).

Currently, European Society of Cardiology (ESC) guidelines suggest that an NT-proBNP of $<125\text{ng/L}$ ($<35\text{ng/L}$ for BNP) excludes chronic heart failure but provide no specific advice on adjustments for age, sex, BMI, renal function or heart rhythm (8). An NT-proBNP of 125ng/L is already several times higher than the average for a healthy person aged <60 years (39, 40). Insurance data from the USA on almost quarter of a million people, who may not always have reported if they had heart disease, found that 91% of men and 74% of women aged <60 years had an NT-proBNP of $\leq 75\text{ng/L}$ and values rarely exceeded 300ng/L in people of either sex aged <80 years (41). However, the relative risk of all-cause mortality increased substantially when NT-proBNP exceeded 75ng/L for all groups other than younger women, possibly an artefact due to small numbers in this group. In an individual-participant-data meta-analysis including almost 100,000 people without prevalent cardiovascular disease, plasma NT-proBNP rarely exceeded 125ng/L in people <80 years (36). In men aged <60 years, the geometric mean plasma NT-proBNP was about 30ng/L , but about 60ng/L for women. Plasma concentrations of NT-proBNP climbed steadily with age thereafter, with the

gap between men and women closing (Figure 2). During a median follow-up of 7.8 years almost 10,000 cardiovascular events had occurred; those with an NT-proBNP >100ng/L had a substantially greater risk of events. A meta-analysis of studies conducted in primary care suggested a diagnostic threshold for HF_rEF of <50ng/L for people aged <50 years, 75ng/L for those aged 50-75 years and 250ng/L for those aged >75 years (42). However, other causes of heart failure and the effects of heart rhythm and renal function on NT-proBNP were not considered that might have improved diagnostic performance still further. Large trials of patients with stable ischaemic heart disease or diabetes suggest that 50% or more will have a plasma NT-proBNP >125ng/L, which is associated with an adverse prognosis, a key aspect of the heart failure syndrome (43, 44). Patients with diabetes, hypertension or coronary artery disease who have an elevated BNP/NT-proBNP, indicating congestion, have higher rates of morbid events and mortality. Surely this fulfils the criteria for a definition of heart failure for those who are not willing to wait until symptoms and signs are also present? Many of these patients would have breathlessness and a reduced exercise capacity if they were asked to do an exercise test. However, there are many causes of breathlessness and exercise intolerance that are not due to cardiac dysfunction, there is a large subjective component to exercise and there are problems with standardising tests, reproducibility and recording of results that do not provide a robust foundation for a diagnosis of heart failure.

ESC guidelines recommend that raised plasma concentrations of BNP/NT-proBNP should not be used to establish a diagnosis of heart failure, stating that “there are numerous cardiovascular and non-cardiovascular causes of elevated natriuretic peptides that may weaken their diagnostic utility in heart failure” (8). However, most problems associated with increases in BNP/NT-proBNP cause cardiovascular dysfunction and congestion and are associated with a poor prognosis. Plasma concentrations of BNP/NT-proBNP rise with age, which may reflect declining diastolic ventricular performance and renal function and the

development of occult or overt cardiovascular disease (40). The risk of dying also increases steeply with age. Using higher threshold values to define disease in older people might not be appropriate, other than as a way of rationing healthcare (45). Women have slightly higher plasma BNP/NT-proBNP but, in general, a better prognosis and therefore some adjustment of diagnostic thresholds for sex seems appropriate, especially for younger women (40). Patients with a higher BMI have lower plasma concentrations of natriuretic peptides but have a better prognosis unless obesity is severe (BMI >40kg/m²) (28). Renal dysfunction is also associated with higher plasma BNP/NT-proBNP, due both to reduced clearance of these peptides and to more severe congestion because of water retention, anaemia, co-existing cardiovascular disease and uraemic cardiomyopathy (39). A raised plasma concentration of BNP/NT-proBNP indicates a poor prognosis precisely because it reflects the adverse impact of both renal and cardiac dysfunction. BNP and NT-proBNP retain their prognostic value even when renal dysfunction is severe (46). Atrial fibrillation also adversely affects prognosis and causes plasma concentrations of natriuretic peptides to rise, either due to the arrhythmia itself or to atrial dilatation and myopathy (47, 48). BNP/NT-proBNP is often elevated in patients who are acutely unwell with sepsis or trauma. Just as an elevation in troponin may indicate myocardial injury (Type-II myocardial infarction), an elevation in BNP/NT-proBNP associated with an acute illness may indicate congestion due to cardiac and renal dysfunction (49). Whether these patients have a form of heart failure (Table 1: Type II heart failure) and would benefit from treatment directed at congestion is untested and should be explored. In summary, elevated plasma concentrations of natriuretic peptides are “bad news”; the cause should be identified, which will usually be congestion associated with cardiac and renal dysfunction.

Plasma concentrations of BNP/NT-proBNP above the diagnostic threshold indicate the need for imaging to confirm the presence of congestion (ie:- atrial dilation) and identify its cause.

If the diagnostic threshold for BNP/NT-proBNP is set high, this will identify a small number of people who have severe disease and a high risk of events. If the threshold is set low, this will identify a large number of people with milder disease and a modest increase in risk. Having different thresholds might be useful depending on whether sensitivity or specificity is the priority. If resources allow, a relatively low actionable threshold would be desirable. Thresholds of 75ng/L or lower may be appropriate for men aged <60 years but higher thresholds for women and older people may be appropriate, perhaps up to 250ng/L for patients of either sex aged >80years (Figure 2 & Table 2). Higher thresholds for BNP/NT-proBNP will have greater specificity but may miss important, treatable disease. Plasma concentrations of BNP/NTproBNP should be interpreted not only with knowledge of age and sex, but also BMI, renal function and heart rhythm. Ultimately, just as glomerular filtration rate can be derived by entering four to six variables into a computer program, so could the expected normal BNP/NT-proBNP for an individual be calculated, substantial deviation from which might be the best method to determine the presence of congestion and the need for further investigation.

The incidence of myocardial infarction and prevalence of diabetes were profoundly affected by changes to their definitions (1, 50). A new definition of heart failure (Table 1; Figure 2) might have a similarly large effect on the incidence and prevalence of heart failure, which might swamp diagnostic services. Moreover, there is still a paucity of evidence that treating patients for heart failure before the onset of symptoms improves outcomes (51, 52). Such considerations did not prevent changes to the definition of either myocardial infarction or diabetes. If raised troponin concentrations (indicative of myocardial injury) were held to the same standard as natriuretic peptides, we might still be measuring the MB band of creatine phosphokinase to diagnose acute myocardial infarction. A robust and objective definition of heart failure will be a catalyst to improve understanding of its epidemiology and treatment.

We should now test the utility of this proposal by conducting clinical trials to demonstrate that interventions can improve the outcome of patients who have few or no symptoms but meet the criteria we propose. Indeed, we have already begun (51, 52); more trials are underway [<https://clinicaltrials.gov/ct2/show/NCT02556450>]. Ultimately, diagnostic criteria are most robust when they benefit patient care, either by helping choose treatments that improve symptoms or prognosis or, by predicting what is likely to happen to the patient and when. Our proposal should stimulate a discussion to agree an objective, verifiable Universal Definition of Heart Failure. Doubtless, as for other diseases, diagnostic criteria will evolve.

Legends to Figures

Figure 1

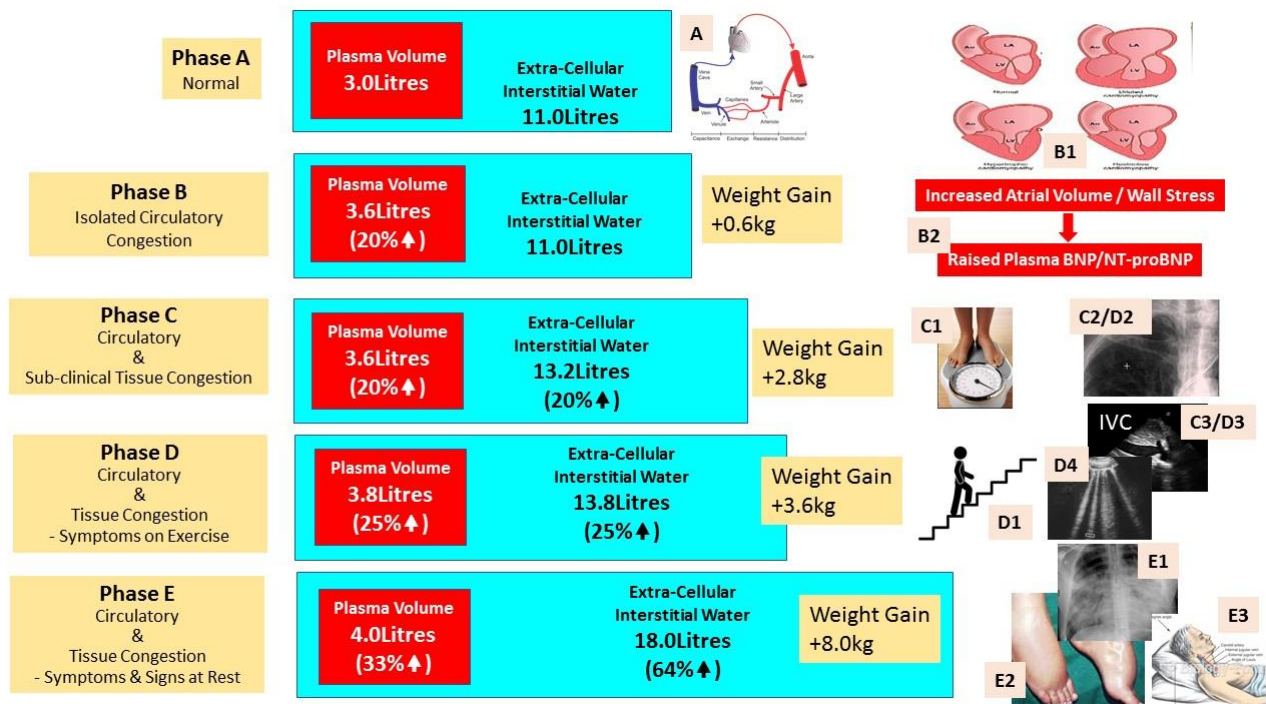


Diagram to Illustrate Different Phases of Congestion

Red boxes indicate approximate plasma volume and blue boxes approximate extra-cellular, tissue water volume for a 75kg person in various clinical states. Note that diuretics may have important and complex effects on the relationship between plasma volume and extra-cellular water that might produce further scenarios. We propose that the definition and diagnosis should not be delayed until Phase D but made at Phase B (a transient state) or Phase C, before the onset of symptoms.

Phase A: Health:

Blood volume is about 5.0L of which 3.0L is plasma. Approximately 70% of the blood volume is in the venous system, 10% in the lung, 10% in the systemic arterial system, 5% in systemic capillaries and about 5% in the four chambers of the heart (A).

Phase B: Isolated Circulatory Congestion:

Defined as expanded plasma volume without an increase in interstitial water. Increased plasma volume leads to atrial distension (B1) and a rise in plasma B-type natriuretic peptides (BNP/NT-proBNP) due to increased wall stress (B2) that increase water and salt secretion to try to restore plasma volume. Circulatory congestion alone should be asymptomatic. This is a transient state because circulatory congestion leads to changes in capillary hydrostatic pressure and an increase in tissue water once any increase in lymphatic drainage is exceeded.

Phase C: Circulatory Congestion with Subclinical Tissue Congestion

Expansion of plasma volume leads to an increase in interstitial water but no obvious symptoms or signs of congestion. The patient may be aware of weight gain (C1). Although the patient reports no symptoms, exercise capacity may be reduced. However, there are many reasons for a reduced exercise capacity and a large subjective component. As congestion progresses, there may be radiological (C2: upper lobe venous diversion) or ultrasound (C3: IVC = inferior vena cava distension) evidence of raised pulmonary or systemic venous pressures, but these may not be obvious until the patient has symptoms (D2/D3).

Phase D: Circulatory Congestion with Tissue Congestion and Symptoms on Exercise

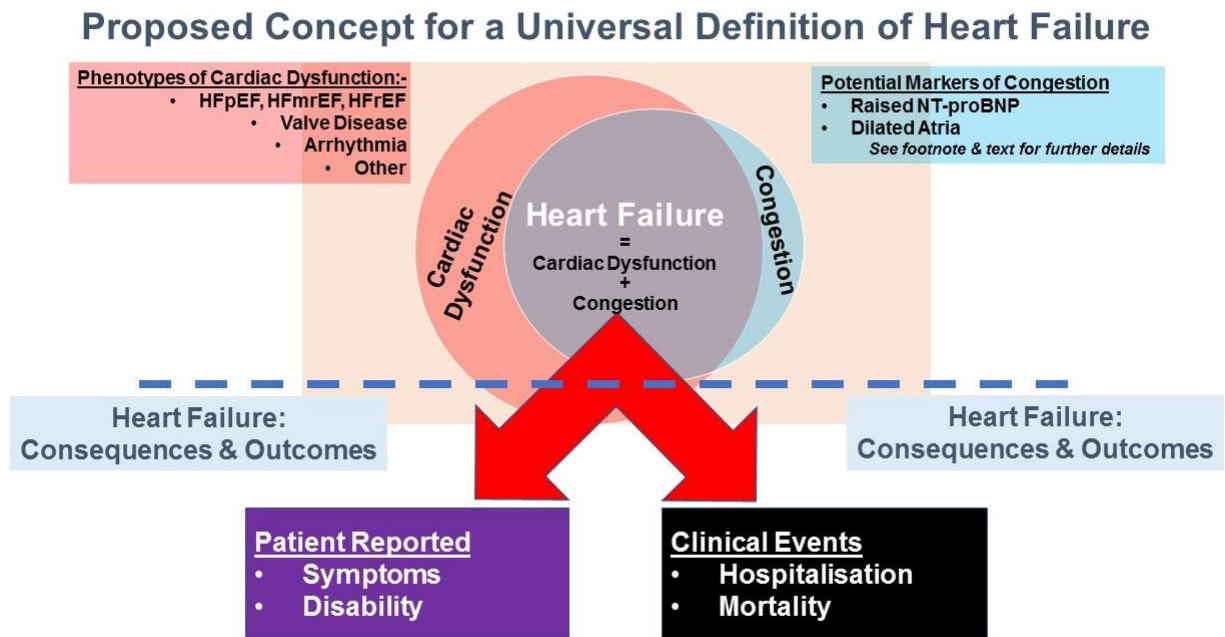
Further expansion of plasma volume and increasing accumulation of interstitial water leads to the development of symptoms on exertion (D1). There may still be no signs of congestion at rest, although the patient may notice that their clothes and shoes are a tighter fit, indicating the development of peripheral oedema. There is increasing evidence of circulatory congestion (D2; D3) and interstitial (B-lines) lung oedema (D4) may be observed.

Phase E: Circulatory with Tissue Congestion and Symptoms & Signs at Rest

Even modest increases in lung water may cause alveolar pulmonary oedema (D1), which will provoke severe breathlessness even at rest. Some patients will swiftly move from Phase A to Phase D (for example rupture of mitral valve leaflets or extensive myocardial infarction), with redistribution of fluid into the lung rather than renal retention of water. However, most

patients are likely to have had long-standing cardiac dysfunction. Systemic congestion occurs more gradually, causing jugular venous distention (D2) and peripheral oedema (D3). Systemic congestion will affect all organs. Hepatic congestion will impair degradation of aldosterone leading to further sodium and water retention. Renal congestion will also exacerbate water and salt retention. Weight gain may exceed 20kg (20 Litres of water) in severe cases.

Figure 2



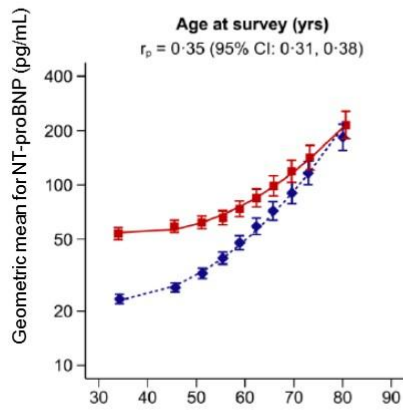
Proposed concept for a universal definition of heart failure comprising cardiac dysfunction (based on imaging) and congestion (based on natriuretic peptides). Plasma concentrations of BNP (B-type natriuretic peptide) and NT-proBNP (the amino-terminal fragment of the pro-peptide) are usually elevated long before symptoms and signs of congestion are apparent. Note that cardiac dysfunction may be due to myocardial disease (*HF_rEF*, *HF_{mr}EF* and *HF_pEF* refer to heart failure with a reduced, mid-range or preserved left ventricular ejection fraction), valve disease, arrhythmia or other rarer problems.

Patients with end-stage renal disease, nephrotic syndrome or severe nutritional disorders can develop congestion but this will usually be complicated by cardiac dysfunction. These causes of congestion can be identified from the medical history and by measuring urine protein and serum creatinine.

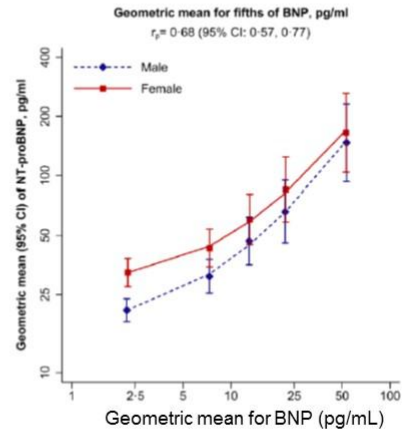
Figure 3

Figure 3

Association between plasma concentrations of NT-proBNP and Age for Women and Men with no history of cardiovascular disease



Association between plasma concentrations of BNP and NT-proBNP in people with no history of cardiovascular disease (adjusted to age 60 years)



Adapted from Reference 23. Natriuretic Peptides Steering Committee: Willeit P et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *Lancet Diabetes Endocrinol* 2016;4(10):840-849.

Relationship between age and NT-proBNP (the amino-terminal fragment of the brain natriuretic peptide pro-peptide) stratified by sex (left hand panel) and between BNP and NT-proBNP stratified by sex (right hand panel) for a meta-analysis including 95,617 participants.

Adapted from Reference 36.

Table 1

UNIVERSAL DEFINITION	
Of Myocardial Infarction	of Heart Failure
Predisposition	Predisposition
Coronary disease in the absence of evidence of myocardial injury	Cardiac dysfunction without congestion
Myocardial Injury	Congestion
An increase in plasma troponin above the upper reference limit (99th Centile)	An increase in plasma natriuretic peptides \diamond and/or atrial dilatation $\diamond\diamond$
Acuity	Acuity
Acute: a non-sustained increase in troponin	Acute: a non-sustained increase in NP
Chronic: a sustained increase in troponin	Chronic: a sustained increase in NP
Myocardial Infarction	Heart Failure
Acute Myocardial Injury (as defined above) with Evidence of Myocardial Ischaemia	Congestion with cardiac dysfunction @
Type-I: due to coronary occlusion (thrombus)	Type-I: cardiac dysfunction is the primary cause of congestion
Type-II: not due to coronary occlusion	Type-II: cardiac dysfunction secondary to another cause of congestion (eg:- renal disease, fluid overload)
Severity of Myocardial Infarction	Severity of Congestion
Myocardial infarction size	Plasma concentration of natriuretic peptide:
Left ventricular ejection fraction	Symptomatic#: Yes/No
Severity of congestion	Treatment with loop diuretics: Yes/No

** not part of the UDMI. NP = natriuretic peptides

@ ventricular or valve disease or atrial dilatation

orthopnoea, undue exertional breathlessness or dependant oedema

\diamond NT-proBNP, BNP or MR-proANP above the upper reference limit for healthy people adjusted for age, sex and BMI from a large healthy population, ideally also excluding patients who develop disease within a few years after testing. Until further information becomes available, an NT-proBNP of >125ng/L (8) or age and sex-related values based on Fulks et al (41) and Hildebrandt et al (42) (table 2) may be used to define values above which congestion might be considered to exist and therefore, in the presence of cardiac dysfunction, heart failure.

$\diamond\diamond$ Left atrial diameter >2.6cm/m² or left atrial volume >33mL/m²

[https://www.echopedia.org/wiki/Normal_Values_of_TTE]

Table 2	Potential Diagnostic Thresholds Stratified by Age & Sex#	
	Men	Women
<60 years	>75ng/L	>125ng/L **
60-69 years	>125ng/L*	>175ng/L **
70-79 years	>175ng/L*	>225ng/L **
>80 years	>250ng/L	>250ng/L

* 50ng/L higher than for previous decade

**50ng/L higher than for men in the same age group.

Proposed thresholds extrapolated from Fulks et al (41) and Hildebrandt et al (42) and require further validation in clinical trials and practice.

Further adjustment for body mass index (BMI) should be considered.

Plasma concentrations will be higher in patients with atrial fibrillation and those with important renal dysfunction. An increased plasma concentration should be interpreted in the context of heart rhythm (an electrocardiogram) and renal function (serum creatinine).

Diagnostic thresholds may be personalised using a combination of age, sex, BMI, heart rhythm and serum creatinine in a calculator similar to that for glomerular filtration rate.

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