Non-Invasive measurement of Right Atrial Pressure by Near-Infrared Spectroscopy: Preliminary Experience. A Report from the SICA-HF Study

Short title: NIRS in heart failure

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Conflict of interest: Mespere donated equipment and JGFC and PP have received honoraria from them for an advisory board.

This is the peer reviewed version of the following article: Pellicori, P. , Clark, A. L., Kallvikbacka-Bennett, A. , Zhang, J. , Urbinati, A. , Monzo, L. , Dierckx, R. , Anker, S. D. and Cleland, J. G. (2017), Non-invasive measurement of right atrial pressure by near-infrared spectroscopy: preliminary experience. A report from the SICA-HF study. Eur J Heart Fail, 19: 883-892, which has been published in final form at https://doi.org/10.1002/ejhf.825. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Abstract

Background: Jugular venous distension, reflecting raised right atrial pressure (RAP), is a classical sign of congestive heart failure (CHF), but its clinical assessment can be difficult.

Methods: RAP was measured non-invasively using near-infrared spectroscopy (NIRS) over the external jugular vein (Venus 1000, Mespere LifeSciences, Canada) in ambulatory patients with CHF enrolled in the "Studies Investigating Co-morbidities Aggravating Heart Failure" (SICA-HF) programme.

Results: Comparing 243 patients with CHF (mean age 71 years; mean left ventricular ejection fraction (LVEF) 45%, median NT-proBNP 788 ng/l) to 49 controls (NTproBNP $\leq$ 125 ng/l), RAP was 7 (IQR: 4-11) versus 4 (IQR: 3-8) mmHg, p<0.001. Those with RAP $\geq$10 mmHg (N=75) were older, had more severe clinical congestion and renal dysfunction, higher plasma NTproBNP, larger left atrial volume, higher systolic pulmonary pressure and were more often in atrial fibrillation but their LVEF was similar to patients with lower RAP.

During a median FU of 595 (IQR: 492-714) days, 49 patients (20%) died or were hospitalized for worsening CHF. Compared to patients with RAP $\leq$5 mmHg, those with RAP $\geq$10 mmHg had a greater risk of an event (HR 2.38, 95% CI: 1.19-4.75, p=0.014). RAP measured by NIRS predicted outcome, competing with NT-proBNP in multivariable models.

Conclusions: Measuring RAP using NIRS identifies ambulatory patients with CHF who have more severe congestion and a worse outcome. The device might be a useful objective method of monitoring RAP, especially for those inexperienced in eliciting physical signs or when measurement of natriuretic peptides is not immediately available.

Key words: heart failure, Near-Infrared Spectroscopy, right atrial pressure, prognosis**.**

Introduction

An increased jugular venous pressure (JVP), reflecting raised right atrial pressure (RAP) is not only a classical sign of congestive heart failure (HF) but also a powerful predictor of an adverse outcome. (1)

When the JVP is raised, expert doctors are likely to make a correct diagnosis of congestion and impaired haemodynamics (2); but assessing the JVP is challenging, and many clinicians are neither familiar with its measurement nor skilled in its interpretation. (3,4) Measurement of inferior vena cava (IVC) or internal jugular vein diameter (JVD) by ultrasound provide an indirect estimate of RAP, and identify with more precision patients with HF who are congested and at high risk of adverse events (5-8); however, these ultrasonic methods require specific probes and trained personnel.

Although the discovery of near-infrared energy dates to the beginning of the 19th century (9), it is only recently that interest in near-infrared spectroscopy (NIRS) has grown as a tool for medical research that might have a wide range of clinical applications (10-12).

NIRS of the external jugular vein allows easy, quick, and non-invasive estimation of RAP. We investigated whether NIRS-derived RAP readings are clinically relevant, by relating them to other clinical, biochemical and ultrasound indices of cardiac dysfunction and congestion, and by assessing their prognostic value in out-patients with HF.

Methods

Study Population

Between April 2013 and April 2014, consecutive control subjects and patients with HF were enrolled in Kingston-Upon-Hull, UK, for the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF, ClinicalTrials.gov Identifier: NCT01872299) (13). SICA-HF is an international observational study of the prevalence, incidence and impact of key co-morbidities in out-patients with a clinical diagnosis of HF. For the purpose of this analysis, we considered patients to have cardiac dysfunction as the likely cause of HF symptoms if they had LVEF ≤50% **or** abnormal NT-proBNP (>125 ng/L) (14). Patients with end-stage renal failure or on renal dialysis, an alternative cause for raised NT-proBNP, were not enrolled in the study.

Controls were subjects aged >60 years who had no history of HF who were recruited to the SICA-HF study by invitation from primary care practice lists, the majority of whom had hypertension or type-2 diabetes. All control subjects had to have normal left ventricular function on echocardiography and a plasma NTproBNP <125 ng/l.

Patients were managed according to contemporary guidelines and assessed after optimisation of their medical therapy. Patients provided a detailed clinical history and blood tests (including haematology, biochemistry profile and NT-proBNP) and had an electrocardiogram and echocardiogram on the same day. Patients in atrial fibrillation or atrial flutter were grouped as "AF".

Patients were followed up until 30th June 2015. The primary outcome of interest was a composite of HF hospitalization or all-cause mortality. Our hospital is the only one in the region offering acute medical services. We have access to all primary and secondary care

records. Outcome is censored at the point of last medical contact in primary or secondary care. Data regarding deaths and hospitalisations were collected from the hospital's electronic systems, supplemented by information from patients, discharge letters and their family doctors. Hospitalisations were considered to be HF-related if the discharge letter suggested HF as a key reason for admission. All data regarding admissions and deaths were entered into a dedicated online database, and were adjudicated at regular intervals by different researchers blind to any other measurement collected at the time of the clinical visit.

The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent.

Clinical examination

Clinical examinations were performed by an experienced doctor (PP) before echocardiography and NIRS evaluation. A clinical congestion score was applied, based on lung auscultation (normal, presence of basal, mid zone or diffuse crackles), JVP (not visible, raised 1-4 cm, raised to earlobe), peripheral oedema (none, ankles, below or above knees) and liver examination (not palpable, palpable) with one point attributed for each degree of severity. Patients with a score of three or more out of a possible score of nine were defined as being congested (15).

NIRS measurements

Following clinical examination and before echocardiography, with the patient reclining and head and neck elevated at 45°, RAP was measured using NIRS (Venus 1000, Mespere LifeSciences, Canada, Figure 1), a portable device that includes adhesive patches connected to a reading electrode placed over the external jugular vein on the right side of the neck and a

reference point aligned with the right atrium (the fourth intercostal space at the mid-antero-posterior diameter of the chest wall). NIRS works by projecting near-infrared light into the neck tissue adjacent to the external jugular vein to detect and analyse reflected light. As the absorption of near-infrared light is mainly by haemoglobin, variations in the amplitude of reflected light are related to pulsations in the superficial external jugular vein. Once the jugular venous pulse is detected, pressure is measured compared to a zero-reference, usually the 4th intercostal space in the mid-antero-posterior diameter of the chest wall. If the height of the JVP is above or below the reading electrode, the device prompts adjustment of the slope at which the patient is lying. Once stable waveforms and readings are obtained, the device records RAP (in mmHg). It takes about two minutes to conduct the test.

Echocardiographic measurements

Echocardiography was performed by a single operator (AB) using a Vivid Seven (GE Health care, UK) system operating at 1.7-3.4MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical and subcostal views. Echocardiograms were stored and reviewed by the same operator blinded to other patient details using an EchoPAC station (GE Health care, UK). LVEF was measured using Simpson's biplane method. LA volume was measured in the four-chamber view and indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess right ventricular (RV) systolic function. The maximum trans-tricuspid systolic gradient was also measured by echocardiography (based on the modified Bernoulli equation, ΔP = Max TR velocity^2 x 4). With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured between one and three centimeters before merger with the right atrium.

Jugular vein ultrasound assessment

We have previously reported the method and reproducibility for measuring JVD ratio. (5,6) With the patient reclining and head and neck elevated at 45°, a linear high-frequency probe (10 MHz) was placed on the left side of the neck below the angle of the jaw and moved inferiorly toward the angle of Louis until the left internal JV was identified. Internal JV diameter and its changes were then measured continuously by M-mode or in the 2-dimensional frame at rest (expiratory phase), during a Valsalva manoeuvre (performed by forceful expiration against a closed glottis) and, finally, during deep inspiration by AB. The ratio between maximum JV diameter during Valsalva and diameter at rest was calculated (JVD ratio).

Statistical methods

Categorical data are presented as percentages; normally distributed continuous data as mean $\pm$ standard deviation (SD) and non-normally distributed variables as median and interquartile range (IQR).

Patients with HF were grouped by normal ($\leq$5 mmHg), borderline (6-9 mmHg) or raised ($\geq$10 mmHg) RAP. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Different multivariable models were tested using a limited number of variables to prevent statistical overfitting. In Model A, we chose, prospectively, five candidate variables of interest (age, NYHA class, creatinine, LVEF and log [NTproBNP]) in addition to RAP; for Model B (biochemical), we selected the biochemical variables that were most strongly

associated with prognosis in univariable analysis, in addition to age, log[NTproBNP] and RAP; for model C (echocardiography) we selected echocardiographic variables strongly associated with outcome in univariable analysis, including and excluding IVC diameter, in addition to age and RAP.

Treatment variables were not included in models as these might be confounded by indication and might vary over time. We did not include mitral and tricuspid regurgitation because their estimation was semi-quantitative and because we included patients with AF, which might make the interpretation of valvular regurgitation difficult. Forward and backward procedures were used to determine which variables independently predicted the primary composite outcome. Assumptions of the models were tested, such as multicolinearity and proportional hazards.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.
All the analyses were performed using SPSS v.22 and Stata software. A 2-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The mean age of patients with CHF (n=243, table 1) was 71 (±10) years, 36% were women, 58% had IHD and 28% had AF. Mean LVEF was 45 (±13)% and median plasma NTproBNP was 788 [280 –1481] ng/l. Approximately 80% of patients were treated with beta-blockers and ACE-inhibitors and 63% were taking loop diuretics.

Amongst controls (n = 49), 84% had diabetes (DM), 69% had hypertension (HTN) and 16% IHD. Their mean age was 72 (±8) years, 49% were men; mean LVEF was 60 (±5)% and median NT-proBNP 72 (45-104) ng/l.

Reproducibility of Measurements of right atrial pressure by NIRS

RAP by NIRS was measured separately by two operators blind to each other's results in 20 patients. The reproducibility of RAP measurements was tested using the Bland-Altman method. Inter-operator reproducibility of RAP was good (Figure 1 supplementary; mean difference for RAP (±SD): 0.3 (±1.8) mmHg; upper and lower limit of agreement: 3.8; -3.2 mmHg, with no value outside limits of agreement). Moving the reference point from the 4th to 3rd intercostal space lead to slightly lower readings (mean 3.4 (4.1) mmHg vs 4.8 (3.6) mmHg, p=0.001), but moving the reference point from the 4th to 5th did not significantly affect results (4.7 (4.4) mmHg vs 4.8 (3.6) mmHg, p=0.68; figure 2 and 3 supplementary for Bland-Altman plots). The distribution of RAP measured by NIRS in patients with HF and controls is shown in a supplementary figure (4).

RAP by NIRS, clinical and echocardiographic findings

RAP by NIRS could be obtained in all patients; RAP was higher in patients with HF than controls. Amongst patients with CHF, those with RAP $\geq$10 mmHg were older, were more symptomatic, had worse renal function and lower haemoglobin, were more likely to have AF and a clinically raised JVP, and had more clinical and biochemical (NTproBNP) signs of congestion (table 1). They had larger left ventricular and atrial volumes, worse right ventricular systolic function, higher systolic pulmonary pressure, greater IVC and JV

diameter (Table 1) and a lower JVD ratio on echocardiography. Patients with more severe mitral or tricuspid regurgitation also had higher RAP (Table 1 supplementary). However, there was no relation between RAP and sex, IHD, diabetes, hypertension or chronic obstructive pulmonary disease (COPD).

Of patients with RAP ≤5 mmHg, 50% had a normal IVC (≤16 mm), 10% had a JVD ratio ≤4 (abnormal) and 17% had a dilated IVC (>20 mm) compared to 12%, 40% and 50% respectively of those with RAP ≥10 mmHg (Table 1).

There was a positive correlation between RAP and age, left atrial volume index, systolic pulmonary pressure, IVC diameter, NTproBNP and JVD at rest and during deep inspiration (and decreasing JVD ratio). There was a negative correlation between RAP and haemoglobin and creatinine (Table 2).

Of patients with RAP ≤5 mmHg, 79 (98%) had a clinically normal JVP and, conversely, of 50 patients who were thought to have a clinically elevated JVP, only one had an RAP by NIRS of <5mmHg. However, 44 patients thought to have a clinically normal JVP had RAP ≥10 mmHg. Amongst patients with a clinically normal JVP, those who had a RAP ≥10 mmHg had a higher plasma NTproBNP and lower haemoglobin, a larger LA and IVC diameter, and higher TR gradient (table 2 supplementary).

Outcome

During a median follow up of 595 (IQ range: 491 - 714) days, there were 49 primary outcomes amongst patients with HF of which 25 first events were HF hospitalisations and 24

were deaths. Overall, there were 27 deaths amongst patients with HF of which 70% were CV. There was one HF hospitalisation amongst the control group and no deaths.

In univariable Cox regression analysis (Table 3), higher JVP assessed clinically, IVC by echocardiography, or RAP by NIRS, were associated with an increased risk of adverse outcome. In multivariable models, increasing log [NTproBNP] (Model A and B), albumin (Model B) and IVC diameter (Model C) were independently related to an adverse outcome, competing with RAP in the models (Table 4).

Compared to patients with RAP <5 mmHg, those with RAP ≥10 mmHg measured by NIRS had a higher risk of an adverse outcome (HR: 2.38, 95% CI: 1.19-4.75, p=0.014, Figure 2).

Compared to patients who had a low JVP both clinically and with NIRS (N= 79), those with low JVP clinically but high RAP with NIRS (N=44) had nearly a two-fold increase risk of death or admission with HF although this did not reach statistical difference (HR: 1.93, 95% CI 0.85-4.37; p=0.12), probably reflecting the low number of patients and events (figure 5 supplementary).

Discussion

Measuring RAP with NIRS identifies out-patients with HF who have more signs of clinical, biochemical or echocardiographic congestion who are at greater risk of an adverse outcome. RAP measured by NIRS also identified patients with more severe congestion amongst those whose JVP was considered to be clinically normal.

A clinically raised JVP has high specificity in the assessment of volume overload but is insensitive. Moreover, inter-observer variability is substantial and dependent on experience and skills (16), the time and care taken to examine the patient, anatomical differences (particularly in the circumference of the neck) and swings in intra-thoracic pressure due to pulmonary disease.

Although the art of physical examination remains the cornerstone of the evaluation of patients with HF (17), it often fails to detect subclinical congestion. In addition, clinical skills may be declining due to changes in training and the widespread availability and use of diagnostic imaging or biological tests (18). In an era dominated by the dilemma of treating increasing numbers of patients with chronic illnesses without a corresponding increase in resources, there is a growing trend to rely on nurses and less experienced doctors to assess and manage patients. Adding measurement of RAP using NIRS, to measurements of weight, heart rate and rhythm, and blood pressure done routinely by clinical assistants can easily be implemented even in a busy clinic. This could help identify patients with residual congestion and a worse prognosis who might benefit from adjustment in therapy. Using measurements of RAP to tailor diuretic dose for individual patients might merely be considered good clinical practice but, as with any new technology, it is important not to jump to conclusions but rather prove that preconceptions are correct.

Assessing IVC or internal jugular venous diameter ultrasonically provides similar diagnostic and prognostic information to measurement of natriuretic peptides, and are valid alternatives to assess patients' fluid status. Measurements of IVC diameter or internal JVD are objective, recordable and reproducible measures of congestion (5-8) that predict outcome.

However, such measurements require additional time, expertise and special probes. Moreover, although echocardiography might be done routinely when the patient is first referred, it will often not be repeated routinely at follow-up clinics. This might allow progression of the underlying disease to be missed. NIRS can also be measured in patients who are unable to cooperate with simple instructions, such as Valsalva or other respiratory manoeuvres, or in frail patients who may not tolerate long and detailed echocardiographic studies.

Limitations

The sample size is relatively small, and the number of events relatively few. Further, larger, multi-centre studies are required to confirm our findings. Although we found good correlations between RAP measured by NIRS and echocardiographic indices of congestion, we did not collect invasive haemodynamic data in our patients. However, others have shown that RAP measured by NIRS is accurate compared to invasive measurements (19).

Although reproducibility was good, we found greater variability for lower RAP measurements, perhaps reflecting difficulties in identifying the jugular vein when RAP is not substantially raised. A potential source of error is the zero-reference placement which might lead to under- or overestimation of readings.

We included a broad range of patients with cardiac dysfunction. Some patients will not have fulfilled enough criteria to be considered to have HF by some experts. However, this analysis was not designed as a diagnostic exercise but rather to investigate the range and significance of RAP measured by NIRS in a relevant population. A population of patients with narrowly defined HF might be considered to be of less interest.

Our control group consisted of many patients with or at high risk of CV disease already receiving ACE-inhibitors, beta-blockers and diuretics; it is possible that treatment had normalised circulating levels of NTproBNP and RAP. Thus, there is likely to be some overlap between patients in the disease and control groups in the present study. We believe that this is a strength, rather than a weakness, since it should be much easier to detect a difference if the control group had been fit, young, healthy individuals. One patient in the control group did subsequently have a HF related hospitalization but many more occurred in patients with HF even when RAP was ≤5 mmHg (similar to controls) (HR 7.59, 95% CI 0.99-58.41, p=0.05).

Conclusions

Evaluation of RAP using NIRS identifies out-patients with heart failure who have a higher risk of an adverse outcome. This device might be used for the rapid bedside evaluation of right atrial pressure and congestion in patients with HF, especially when it cannot be assessed confidently by clinicians and measurement of natriuretic peptides are not immediately available.

Funding

The research leading to these results has received funding from the European Union Seventh Framework Programme [FP7/2007-2013] under grant agreement n° 241558 (SICA-HF).

The research leading to these results has received funding from the Russian Ministry of Science and Education within the FTP "R&D in priority fields of the S&T complex of Russia 2007-2012" under state contract °02.527.11.0007.

Conflict of interest: Mespere donated equipment and JGFC and PP have received honoraria from them for an advisory board.

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Legend to figures

Figure 1. Measurement of right atrial pressure (RAP) using Near-Infrared Spectroscopy (NIRS**)**. With the patient reclining and head and neck elevated at 45°, the external jugular vein (JV) was identified and RAP measured using NIRS (Venus 1000, Mespere LifeSciences, Canada), a portable device that includes adhesive patches connected to a reading electrode placed over the external JV on the right side of the neck and a reference point aligned with the RA (the fourth intercostal space at the mid-antero-posterior diameter of the chest wall). Once stable waveforms and readings are obtained, the device records RAP (in mmHg)

Figure 2. Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations. Compared to those with normal RAP by NIRS (≤5 mmHg, in red), HF patients with high RAP (≥10 mmHg, in yellow) had more than a 2-fold higher risk of dying or being hospitalised for heart failure (HR: 2.38, 95% CI: 1.19-4.75, p=0.014).

Figure 1, 2 and 3 supplementary: inter-operator reproducibility of RAP measurements by NIRS, and reproducibility by different intercostal spaces (3^{rd} vs 4^{th} and 4^{th} vs 5^{th}).

Figure 4 supplementary: The distribution of RAP by NIRS in patients without (left panel) or with (right panel) heart failure (HF).

Figure 5 supplementary: Kaplan-Meier (KM) curves for the primary composite endpoint (HF hospitalization or death) in patients with heart failure and 'normal/low' JVP both clinically and with NIRS (≤5 mmHg; solid blue line), with HF and clinically 'normal/low' JVP (=0) but high RAP by NIRS (≥10 mmHg; solid green line) and with HF and clinically raised JVP (≥1) and RAP (>5 mmHg). Compared to those with 'normal/low' JVP (both clinically and with NIRS), those with clinically 'normal/low' JVP but raised RAP by NIRS

had around a 2-fold increase in the risk of an adverse outcome, although the difference did not reach statistically significance. Those with clinically high JVP and high RAP by NIRS had the worst outcome.