Monitoring of heart failure: comparison of left atrial pressure with intrathoracic impedance and natriuretic peptide measurements in an experimental model of ovine heart failure

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ABSTRACT

Monitoring of HF (heart failure) with intracardiac pressure, intrathoracic impedance and/or natriuretic peptide levels has been advocated. We aimed to investigate possible differences in the response patterns of each of these monitoring modalities during HF decompensation that may have an impact on the potential for early therapeutic intervention. Six sheep were implanted with a LAP (left atrial pressure) sensor and a CRT-D (cardiac resynchronization therapy defibrillator) capable of monitoring impedance along six lead configuration vectors. An estimate of A_{LAP} (LAP from admittance) was determined by linear regression. HF was induced by rapid ventricular pacing at 180 and 220 bpm (beats/min) for a week each, followed by a third week with daily pacing suspensions for increasing durations (1–5 h). Incremental pacing induced progressively severe HF reflected in increases in LAP (5.9 $\pm$ 0.4 to 24.5 $\pm$ 1.6 mmHg) and plasma atrial (20 $\pm$ 3 to 197 $\pm$ 36 pmol/l) and B-type natriuretic peptide (3.7 $\pm$ 0.7 to 32.7 $\pm$ 5.4 pmol/l) (all $P < 0.001$) levels. All impedance vectors decreased in proportion to HF severity (all $P < 0.001$), with the LV_{ring} (left ventricular)-case vector correlating best with LAP ($r^2 = 0.63$, $P < 0.001$). Natriuretic peptides closely paralleled rapid acute changes in LAP during alterations in pacing ($P < 0.001$), whereas impedance changes were delayed relative to LAP. A_{LAP} exhibited good agreement with LAP. In summary, impedance measured with an LV lead correlates significantly with changes in LAP, but exhibits a delayed response to acute alterations. Natriuretic peptides respond rapidly to acute LAP changes. Direct LAP, impedance and natriuretic peptide measurements all show promise as early indicators of worsening HF. A_{LAP} provides an estimate of LAP that may be clinically useful.

INTRODUCTION

HF (heart failure) is one of the most common causes for hospitalization in the western world and is associated with high morbidity, mortality and economic costs [1]. Despite treatment advances and more intensive clinical monitoring, rehospitalization due to acute decompensation of HF remains high, with pulmonary

Key words: haemodynamics, heart failure, implantable monitor, intrathoracic impedance, left atrial pressure, natriuretic peptide.

Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; bpm, beats/min; CRT-D, cardiac resynchronization therapy defibrillator; HF, heart failure; ICU, intensive care unit; LAP, left atrial pressure; A_{LAP}, LAP from admittance; LV, left ventricular; LVEDV, LV end-diastolic volume; MR, mitral valve regurgitation; PAM^{TM}, Patient Advisor Module; RA, right atrial; RV, right ventricular; Z, intrathoracic impedance.

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congestion being the most common precipitant for re-admission [2]. It has been shown that haemodynamic deterioration may precede the development of severe symptoms of pulmonary congestion and acute HF hospitalization by up to 2 weeks [3,4]. Early detection of decompensation may provide an opportunity for a therapeutic intervention that could prevent hospitalization and potentially improve both quality of life and survival. Clinical experience and recent studies evaluating the use of standard clinical parameters such as weight gain or symptoms demonstrate a lack of sensitivity in detecting decompensation and thus a limited utility for reducing hospitalization [5]. Incorporating implantable sensors or biomarkers into the monitoring strategy could potentially facilitate early detection of clinical decompensation.

LAP (left atrial pressure) is a sensitive indicator of heart function, and elevated LAP leads directly to pulmonary congestion and oedema. Previous studies using surrogate estimates for LAP derived from RV (right ventricular) indices suggest there may be a role for such haemodynamic monitoring in HF management [4,6]. Indeed, recent work using directly measured LAP found that a physician-directed patient self-management therapeutic paradigm guided by daily LAP measurements in ambulatory HF patients was associated with improved clinical status and fewer hospitalizations [7]. A growing number of HF patients are receiving implantable CRT (cardiac resynchronization therapy) devices with or without defibrillators [CRT-D (cardiac resynchronization therapy defibrillator]. In addition to acting as pacemakers and defibrillators, newer CRT-D systems have the capability of measuring *Z* (intrathoracic impedance), which can be used as an indicator of fluid volume status. With worsening HF, increasing intracardiac and intrathoracic fluid volumes results in a fall in intrathoracic impedance. Initial attempts to measure intrathoracic impedance using the RV lead to detect pulmonary oedema in HF patients proved feasible, but demonstrated suboptimal sensitivity and specificity [4,8]. A recent study in dogs demonstrated that intrathoracic impedance vectors derived from a LV (left ventricular) lead are responsive to physiological changes during HF and may provide opportunity for improved sensitivity and specificity in detecting increasing intracardiac and intrathoracic fluid volumes [9]. Since acute changes in LAP are associated with changes in intracardiac and ultimately intrathoracic fluid volumes, there is potential for deriving an estimate of LAP based on intrathoracic impedance measurements.

Plasma levels of the cardiac natriuretic peptides [ANP and BNP (atrial and B-type natriuretic peptide), respectively] reflect cardiac function and clinical status in HF and have also been advocated for HF monitoring [10,11]. Their role in both monitoring and guiding therapy in HF is still the subject of some debate and of ongoing study [12–14]. An improved understanding of the dynamic relationship between LAP and circulating levels of the natriuretic peptides is necessary to fully implement serial ANP/BNP measurements in management of HF.

Using a validated pacing-induced HF model in sheep, we compared for the first time the efficacy of direct LAP, intrathoracic impedance and natriuretic peptide measurements as early indicators of worsening cardiac function and their ability to detect acute changes. We investigated the hypothesis that intrathoracic impedance signals derived from the LV lead of a CRT-D device correlate with LAP and can indicate worsening HF. Since natriuretic peptide levels are also known to reflect changes in fluid volume status [5,10,11], we compared the response patterns in intrathoracic impedance measurements and in natriuretic peptide levels with acute changes in LAP. We also explored the feasibility of estimating LAP from intrathoracic impedance measurements.

MATERIALS AND METHODS

Ethics

The study protocol was approved by the Animal Ethics Committee of the University of Otago, Christchurch, New Zealand.

Implantation procedure and devices

Six sheep were implanted via the right jugular vein with an LAP sensor (HeartPOD^{TM} ISL) and three transvenous bipolar pacing leads [RA (right atrial) – Tendril^{TM} 1688T; RV – Riata^{TM} 1582; LV – QuickSite^{TM} 1056T]. The three pacing leads were attached to a subcutaneously implanted CRT-D (Promote^{TM} RF). The implant procedures were all performed under general anaesthesia (thiopentone for induction; halothane/nitrous oxide inhalation for maintenance) using fluoroscopic guidance. All implanted devices were manufactured by Cardiac Rhythm Management Division, St Jude Medical (Sylmar, CA, U.S.A.).

As described previously [15], the LAP sensor was implanted into the left atrium by trans-septal catheterization and provided direct LAP waveform measurements, along with a corresponding far-field intracardiac electrocardiogram. The LAP sensor was attached to an implantable subcutaneous antenna coil that communicated via telemetry the LAP data to a handheld computer [PAM^{TM} (Patient Advisor Module)]. The data stored on the handheld PAM^{TM} was uploaded on to a computer for further analysis. Implantation of the HeartPOD allowed measurement of direct LAP throughout the study without the need for long-term or intermittent pulmonary artery catheterization (with

associated increased risk of infection, bleeding and other complications).

As reported previously [9], the CRT-D is capable of acquiring continuous measurements of intrathoracic impedance along six lead configuration vectors (LV_{ring}-case; LV_{ring}–RV_{ring}; LV_{ring}–RA_{ring}; RV_{ring}-case; RA_{ring}-case; and RV_{coil}-case) at a fixed measurement interval. Stored measurements were automatically transferred through wireless communication to a computer for further analysis.

A polyethylene catheter (15 guage) was inserted percutaneously into the left jugular vein for subsequent blood sampling.

Study protocol

Following device implantation, the sheep were rested for a 5–10-week period, while the impedance measurements stabilized across all vectors (stabilization period). The sheep then underwent a week of non-pacing baseline recordings (baseline period: study day −7 to day −1) before initiation of 7 days of rapid RV pacing at 180 bpm (beats/min) (days 0–6) followed by 14 days at 220 bpm (days 7–20) to induce progressively severe HF [16]. During the third week of pacing (days 14–18), pacing at 220 bpm was suspended each day for increasing lengths of time – starting from 1 h on the first day and increasing sequentially to 5 h on the fifth day. Pacing was permanently discontinued on day 21, and the sheep were monitored for an additional 12 days (recovery period: days 21–32).

Data acquisition and processing

Intrathoracic impedance data were automatically collected at hourly intervals throughout the study. Impedance vectors were accepted for further analysis if there was an absence of a lead disturbance artifact, which was detected when there was a significant instability in the impedance measurements (>80 Ω) between those obtained at the onset of the protocol (baseline period) and those obtained following the recovery period (beyond day 32). Admittance was calculated as the reciprocal of the measured intrathoracic impedance (admittance = 1/Z). The relationship between admittance and LAP was evaluated using linear regression for each of the vectors. The equation describing the line of best fit between admittance and LAP was utilized to derive estimates of LAP from admittance (A_{LAP}). The relationship between admittance and LAP was compared with the relationship between natriuretic peptide levels and LAP.

LAP measurements were recorded in triplicate daily throughout the study protocol and more frequently (hourly for 6–10 h) on those days when the pacing rate was altered. LAP was calculated by subtracting an atmospheric reference pressure measured by an external sensor located in the handheld PAM™ from the absolute pressure measured directly from the sensor implanted inside the left atrium.

Venous blood samples were drawn throughout the study protocol (immediately after LAP measurements) into EDTA-treated tubes on ice, centrifuged at 4 °C and stored at −80 °C before assay for plasma ANP and BNP as described previously [16].

Statistics

LAP, natriuretic peptide and admittance results are expressed as means ± S.E.M. Effect of pacing on these variables was assessed using one-way repeated measures ANOVA. Where significant differences were identified by ANOVA, the level of significance between baseline and the individual time points was determined by Fisher's protected least-significant difference tests. General linear models (regression) were used to determine the strength of the relationship between LAP and (i) admittance derived from two representative intrathoracic impedance vectors (LV_{ring}-case and RV_{coil}-case), (ii) ANP and (iii) BNP. The models evaluated the relationships during periods of time when LAP was changing gradually over an extended term as well as rapidly over a short term. The long-term analysis was performed using all of the data from the entire study protocol, while the short-term analysis used the data from the third week of pacing when there were acute changes in LAP as pacing was suspended for increasing durations of time. A value of $P < 0.05$ was considered statistically significant. P values were corrected for multiple comparisons when appropriate. Bland–Altman plots were used to analyse the agreement of direct LAP measurements and A_{LAP} estimated from admittance.

RESULTS

Pacing-induced HF model

Incremental pacing induced progressively severe HF as indicated by rises in LAP from a prepacing baseline of 5.9 ± 0.4 to 15.3 ± 1.0 mmHg following a week of pacing at 180 bpm ($P < 0.001$) and to 24.5 ± 1.6 mmHg after a second week pacing at 220 bpm ($P < 0.001$) (Figure 1). LAP levels did not increase further during the third week when pacing at 220 bpm was suspended daily for 1–5 h. Figure 2 shows representative LAP waveform data from one sheep with corresponding electrograms during the various periods of the study protocol. Part of the mechanism for producing an elevation in LAP during rapid ventricular pacing appears to be cannon *A*-waves that represent a simultaneous atrial and ventricular contraction. An acute change in LAP from 24.7 to 14.5 mmHg following cessation of pacing during the third week of pacing (days 14–18) with the disappearance of cannon *A*-waves occurring within 3 min of pacing discontinuation is shown (Figures 2C and 2D). The

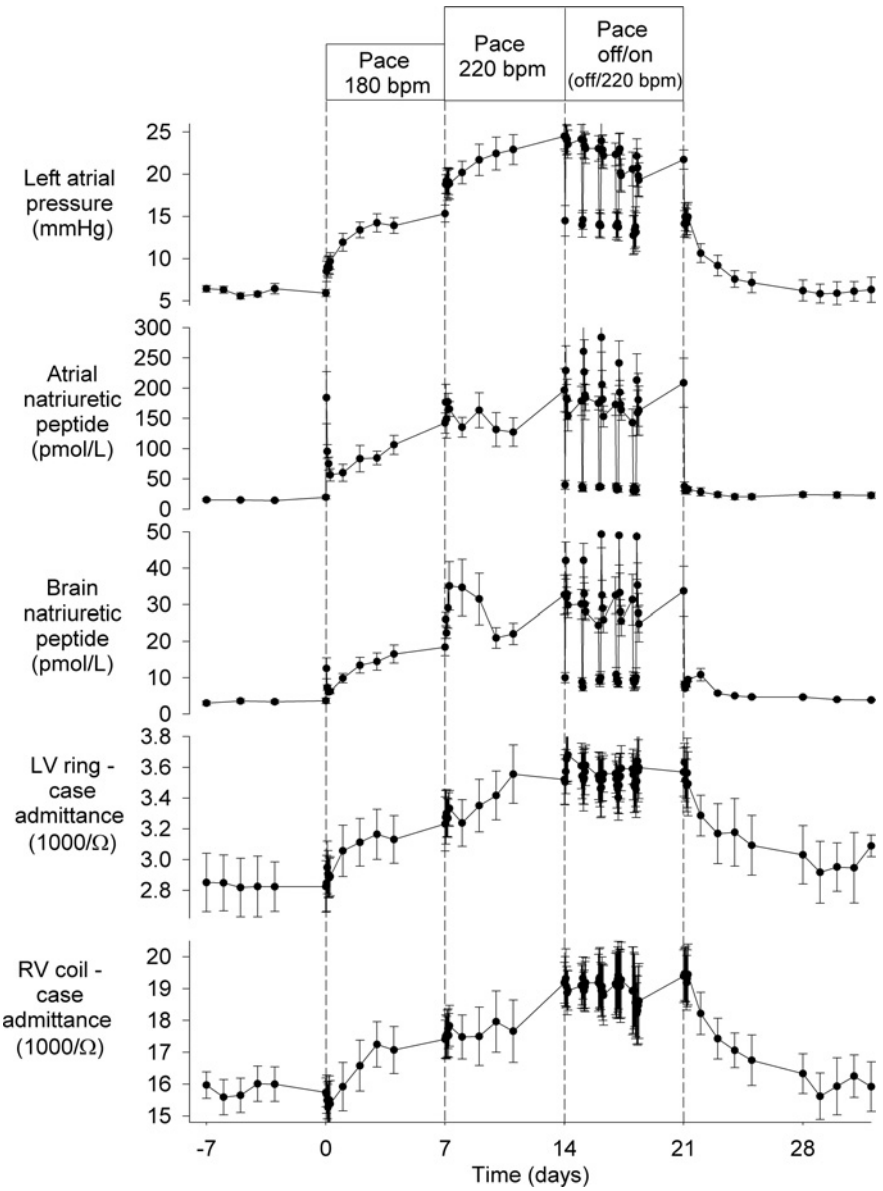

Figure 1 LAP, natriuretic peptide and LV_{ring}-case and RV_{coil}-case admittance vector responses in six sheep during acute and chronic changes in pacing

Values shown are means ± S.E.M.

permanent termination of pacing (day 21) resulted in the gradual reduction of LAP to pre-pacing baseline levels over the subsequent 4 days (Figure 1).

Intrathoracic impedance vectors

Impedance measured across all six lead configuration vectors tended to decrease with the onset and increasing severity of HF and then return towards baseline values on cessation of pacing. Sample raw data from one sheep are shown in Figure 3.

Linear regression analysis between admittance and LAP across all sheep for the entire study duration demonstrated that vectors that utilized the LV_{ring} electrode (LV_{ring}-case, $r^2 = 0.63$; LV_{ring}–RV_{ring}, $r^2 = 0.52$ and LV_{ring}–RA_{ring}, $r^2 = 0.50$) had the strongest correlation with LAP, vectors that utilized the RV electrodes (RV_{ring}-case, $r^2 = 0.50$ and RV_{coil}-case, $r^2 = 0.50$) had a somewhat reduced correlation, and vectors that utilized the RA_{ring} electrode (RA_{ring}-case, $r^2 = 0.33$) had the weakest correlation. The LV_{ring}-case vector and the RV_{coil}-case vector were selected to represent intrathoracic impedance for further analysis. Results for the LV_{ring}-case vector are available for $n = 5$ (data from one sheep excluded due to late instability in impedance measurements), while results for RV_{coil}-case are available for all six sheep.

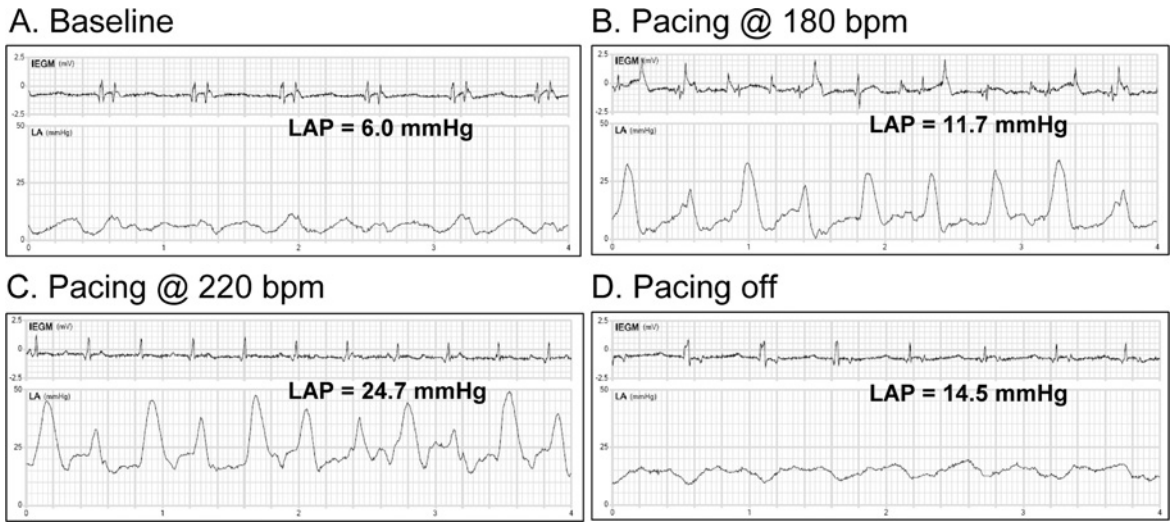

Figure 2 Sample data from one sheep showing LAP waveforms and intracardiac electrogram during the various phases of the pacing protocol

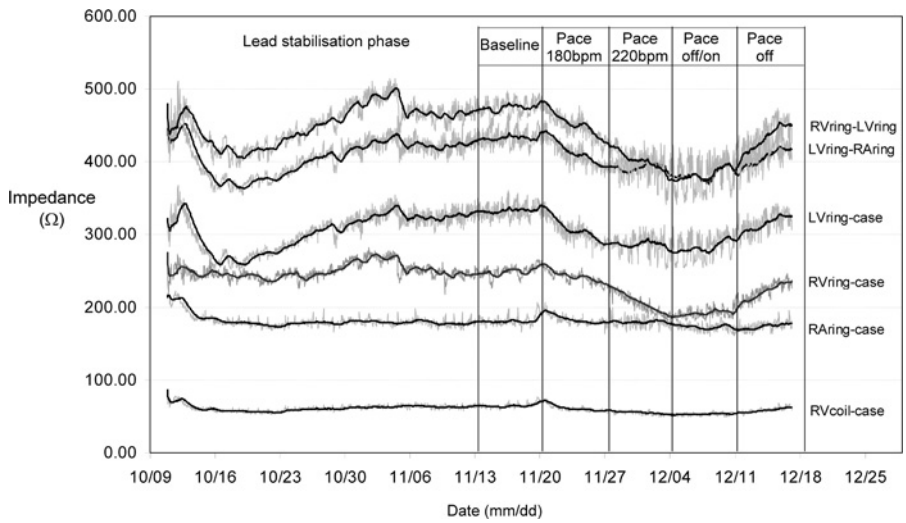

Figure 3 Sample data from one sheep showing intrathoracic impedance trends for the six vectors in response to sequential right ventricular pacing

Long-term trend analysis

Figure 1 shows the trends in LAP, admittance and natriuretic peptide levels over the entire study protocol averaged over all sheep. Rises in LAP in response to incremental pacing were mirrored by LV_{ring}-case admittance, which rose significantly from a pre-pacing baseline of 2.8 ± 0.19 (1000/Ω) to 3.22 ± 0.17 (1000/Ω) (15.0 %; $P < 0.001$) following 1 week of pacing at 180 bpm and to 3.54 ± 0.17 (1000/Ω) (26.4 %; $P < 0.001$) after a further week of pacing at 220 bpm. The RV_{coil}-case admittance also changed significantly across all pacing periods, increasing from a baseline of 15.97 ± 0.42 (1000/Ω) to 17.41 ± 0.60 (1000/Ω) (9.0 %, 180 bpm; $P < 0.05$) and to 19.18 ± 0.64 (1000/Ω) (20.1 %, 220 bpm; $P < 0.001$). Similar to LAP, admittance levels for both the LV_{ring}-case and the RV_{coil}-case vectors were sustained during the third week of pacing. On permanent cessation of pacing, both LV_{ring}-case and RV_{coil}-case admittance returned to pre-pacing baseline levels by 1 week (day 28), a response also similar to, but somewhat slower than, that of LAP.

A comparable overall trend was observed for plasma natriuretic peptide levels over the course of the study as LAP varied following alterations in pacing (Figure 1). In response to progressively increasing LAP, there were approx. 10-fold elevations in plasma natriuretic peptide levels, with BNP increasing from a prepacing baseline concentration of 3.7 ± 0.7 pmol/l (13.2 ± 2 pg/ml) to 18.4 ± 2.4 pmol/l (64 ± 8 pg/ml) (180 bpm; $P < 0.001$) after 1 week and to 32.7 ± 5.4 pmol/l (113 ± 19 pg/ml)

Table 1 Summary of the general linear model results correlating LAP with plasma ANP and BNP, and LV and RV admittance vectors

NS, not significant.

Parameter	Long-term analysis Entire protocol	Short-term analysis Third week of pacing
Plasma ANP	$P = 0.003$	$P < 0.001$
Plasma BNP	NS ($P = 0.084$)	$P < 0.001$
LV_{ring}-case admittance	$P < 0.001$	$P < 0.001$
RV_{coil}-case admittance	$P < 0.001$	NS

(220 bpm; $P < 0.001$) following 2 weeks of pacing. Similarly, ANP rose from a baseline of 20 ± 3 to 142 ± 17 pmol/l (180 bpm; $P < 0.001$) and to 197 ± 36 pmol/l (220 bpm; $P < 0.001$). During the third week of pacing, natriuretic peptide levels were also maintained. The permanent termination of pacing (day 21) resulted in a rapid decline in plasma ANP and BNP to baseline levels within 2 days, a shorter duration compared with LAP. The trend data also demonstrated the presence of an 'overshoot' in ANP and BNP levels upon the initiation of rapid pacing (day 0) and upon increasing the pacing rate to 220 bpm (day 7). The latter overshoot for ANP was apparent for less than a day, while for BNP, it extended to 3 days before declining.

Analyses across the entire study protocol using all time points revealed that LAP correlated significantly with LV_{ring}-case admittance, RV_{coil}-case admittance and ANP (Table 1). A similar trend was evident for BNP (Table 1), but it is likely that the differences in responses during the first 220-bpm pacing week between LAP (steady rise) and BNP (3-day overshoot and decline) negatively affected the relationship.

Short-term trend analysis

During the third week of pacing (days 14–18), acute interruptions in pacing for increasing durations of time (1–5 h sequentially over the 5 days) induced rapid falls (within an hour) in LAP averaging 9.1 ± 0.1 mmHg ($P < 0.001$) (Figure 4). Recommencement of pacing on each day restored LAP promptly to levels observed prior to pacing termination. Changes in plasma natriuretic peptide concentrations over this 5-day period largely paralleled those of LAP, with ANP and BNP falling on average by 137 ± 8 and 20.9 ± 1.5 pmol/l, respectively (both $P < 0.001$), following disruption of pacing. However, pacing resumption resulted in a striking peak and 'overshoot' in the first hour followed by a re-establishment of ANP and BNP at levels observed prior to pacing cessation.

LV_{ring}-case admittance also showed significant changes across this week ($P < 0.001$), decreasing with pacing suspension and rising on pacing resumption (Figure 4). However, the rate and relative magnitude of changes in admittance were markedly less than those observed for LAP, ANP and BNP. In contrast, RV_{coil}-case admittance showed no significant changes (falls or rises) across this off/on pacing week (Figure 4).

Analyses limited to the third week of pacing showed that LAP correlated well with LV_{ring}-case admittance, BNP and ANP, but not with RV_{coil}-case admittance (Table 1).

Estimated A_{LAP}

Figure 5 shows the relationship between admittance and LAP for the LV_{ring}-case and RV_{coil}-case impedance vectors. For both vectors, the relationship of admittance to LAP displays a hysteresis (retardation of response) both as LAP rises and falls. Of note, data recorded while pacing is on generally falls to the left of (above) the line of best fit, whereas data recorded when pacing is off falls to the right of (below) the line of best fit. Despite the hysteresis and clear separation of data from the 'pacing-on' phases relative to 'pacing-off' phases, linear regression still resulted in a positive correlation of admittance to LAP with r^2 values of 0.63 and 0.50 for LV_{ring}-case and RV_{coil}-case vectors, respectively.

To assess the degree to which a simple linear model may be used to derive estimates of LAP from admittance, the equations describing the line of best fit were then used to calculate A_{LAP} (Figure 5). Bland–Altman plots (Figure 6) were used to assess the agreement between LAP and A_{LAP}. For LV_{ring}-case and RV_{coil}-case vectors, 2 S.D. of the error between A_{LAP} and LAP equated to 8.3 and 9.6 mmHg, respectively. Results for other vectors (results not shown) were as follows: LV_{ring}-RA_{ring} = 8.7 mmHg, LV_{ring}–RV_{ring} = 9.2 mmHg, RA_{ring}-case = 10.3 mmHg and RV_{ring}-case = 9.9 mmHg.

DISCUSSION

Reducing the burden of HF hospitalizations remains a critical problem for chronic HF patients and the physicians who manage them. Improved strategies for haemodynamic and fluid volume monitoring, combined with earlier intervention in response to increasing filling pressures and fluid volumes, are needed to avoid and to interrupt the development of acute decompensation in chronic HF. The present study examined the relationship between intrathoracic impedance signals derived from a CRT-D device and direct LAP measurements acquired with a permanently implantable LAP monitor over acute and chronic alterations in HF severity. The study also compared the response patterns in intrathoracic impedance and in natriuretic peptide levels with changes in LAP. We found that LAP increased over several weeks into the range expected to produce pulmonary congestion in response to rapid ventricular pacing [16]. Changes in ANP and BNP concentrations, as well as the rapidity of the response, generally mirrored those of LAP across all

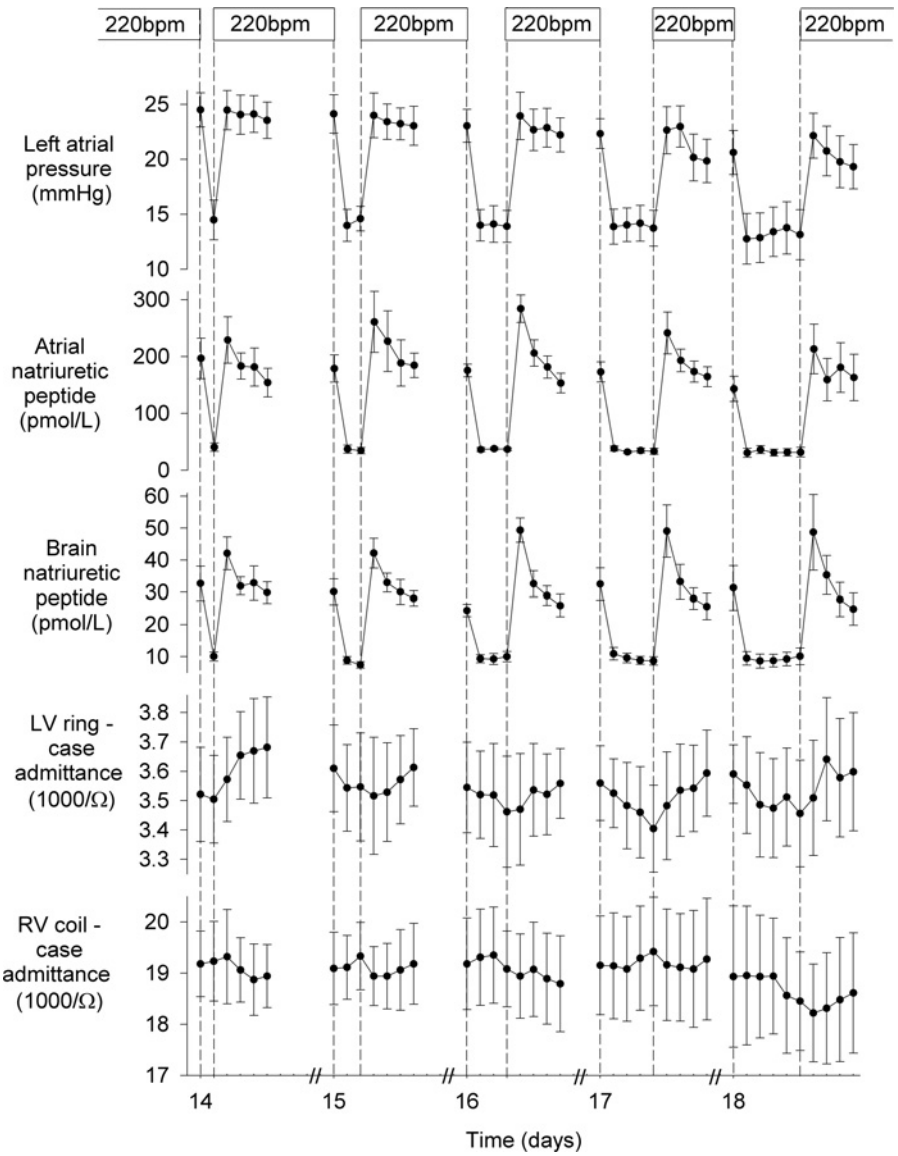

Figure 4 **Expanded view of LAP, natriuretic peptide and LV_{ring}-case and RV_{coil}-case admittance vector responses in six sheep during acute on/off changes in pacing**

Pacing was turned off for a 1-h period on day 14, increasing incrementally each day to a 5-h period on day 18. Values shown are means ± S.E.M.

phases of the study. All six impedance vectors decreased in response to rapid ventricular pacing, with vectors utilizing the LV lead exhibiting the best correlation with LAP ($r^2 = 0.63$) and vectors utilizing the RV lead demonstrating a somewhat reduced correlation with LAP ($r^2 = 0.50$). This is the first study to assess the feasibility of estimating LAP from intrathoracic admittance (A_{LAP}), with results demonstrating a close relationship between the two variables (LAP and A_{LAP}).

Intrathoracic impedance

The long-term trends seen in the present study with intrathoracic impedance decreasing in response to rapid ventricular pacing are consistent with earlier studies [4,8,9]. Similar to our findings, prior work in a canine model of pacing-induced HF [9], where HF progression was monitored with either an LAP pressure sensor or LVEDV (LV end-diastolic volume) measurements via echocardiography, demonstrated that intrathoracic impedance using the LV_{ring}-case vector had the fastest and largest change in response to HF severity and increasing LAP. This earlier study additionally found that LV_{ring}-case impedance measurements had a statistically significant inverse correlation with LVEDV, while impedance using the RV_{ring}-case and RV_{coil}-case vectors did not correlate with LVEDV. These results indicate that LV_{ring}-case impedance measurements may reflect not only LAP, but also LVEDV.

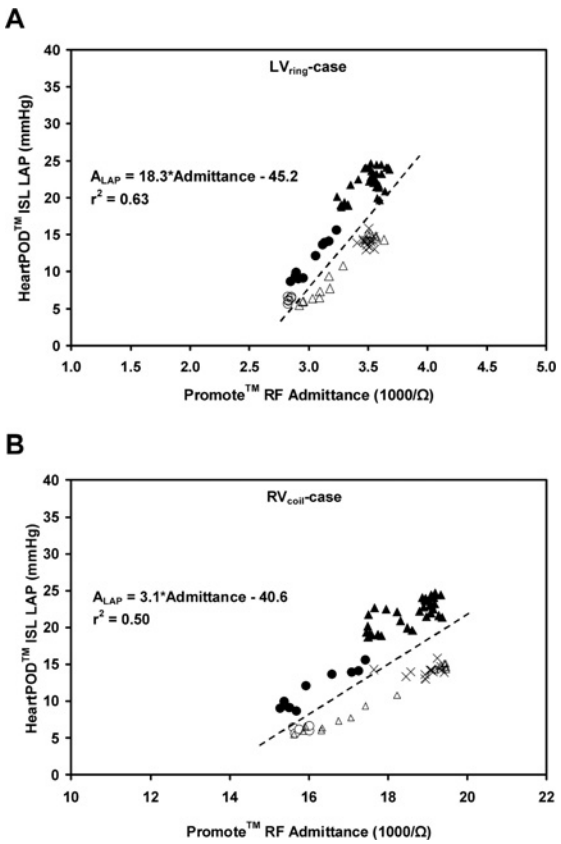

Figure 5 Linear regression of HeartPOD^{TM} ISL LAP recordings compared with Promote^{TM} RF CRT-D admittance for (A) the LV$_{ring}$-case and (B) RV$_{coil}$-case impedance vectors

Data points are from across the experimental phases of the study as follows: ○, baseline (no pacing); ●, pacing (180 bpm); ▲, pacing (220 bpm); ×, pacing off (1–5 h) during on/off week; △, recovery (no pacing). Estimated LAP from impedance (A_{LAP}) is calculated from the admittance using the slope and intercept of the linear regression equation.

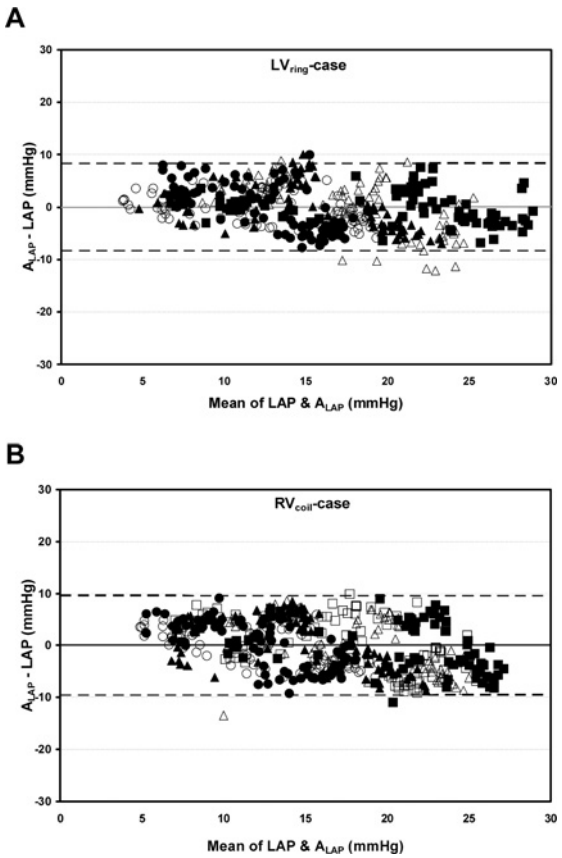

Figure 6 Bland–Altman plots for estimated A_{LAP} compared with LAP measured directly by the HeartPOD^{TM} ISL for (A) LV$_{ring}$-case and (B) RV$_{coil}$-case vectors

LV$_{ring}$-case, 402 data points from five individual sheep; and RV$_{coil}$-case, 485 data points from six individual sheep each shown by different symbols. Broken lines show the ± 2 S.D. of the difference between the two methods which were 8.3 mmHg for LV$_{ring}$-case and 9.6 mmHg for RV$_{coil}$-case vectors.

The present study expands on the prior work by also examining the short-term trends seen in intrathoracic impedance in response to acute changes in LAP and by comparing the response pattern to that seen with the natriuretic peptides. We found that the LV$_{ring}$-case impedance vector also had the best correlation with LAP over short-term durations when abrupt changes in pacing were being performed, but unlike the natriuretic peptides, there was a delay (several hours to 1 day) in the response resulting in a hysteresis-type pattern on the correlation plots, as well as a blunting of the response relative to ANP and BNP. In contrast, the RV$_{coil}$-case vector showed no immediate change within a period of 1–5 h to acute changes of LAP, but did ultimately return to baseline over a longer time interval once pacing was terminated permanently.

Mechanistic hypothesis for hysteresis

The hysteresis seen between admittance (1/*Z*) and LAP may be a consequence of admittance reflecting a volume measurement rather than a direct pressure measurement. Changes in fluid volume distribution occur more gradually relative to changes in intracardiac pressure, which may rapidly develop with acute alterations in venous capacitance (preload), vascular tone (afterload), contractility, valvular function and/or rhythm. In the present physiological study, it was noted that part of the mechanism for producing acute changes in LAP was the occurrence and disappearance of cannon *A*-waves with the initiation and termination of rapid ventricular pacing. When rapid pacing was sustained, LAP continued to climb with intracardiac fluid volume, and ultimately fluid volumes within the intrathoracic space were gradually increasing, which resulted in a strong correlation with LAP over a long-term time interval. When rapid ventricular pacing was abruptly

stopped, there was an immediate disappearance of cannon *A*-waves, but intracardiac and intrathoracic fluid volumes did not instantly decrease, but instead, gradually declined with a lag relative to LAP. The present study suggests that the admittance measurements derived from the implanted CRT-D device more likely reflect intracardiac and intrathoracic fluid volumes rather than LAP. The proposed mechanistic hypothesis is further supported by an earlier study performed using a canine model of pacing-induced HF where LVEDV exhibited a delayed response to rapid RV pacing in comparison with the response seen in pulmonary capillary wedge pressure [17].

The hysteresis described in the present ovine study is similar to the pattern expected to occur in patients with functional MR (mitral valve regurgitation) [18]. In these patients, an acute change in afterload and/or papillary muscle perfusion may produce an acute episode of MR, which will result in an immediate increase in LAP followed by a gradual and delayed increase in intracardiac and intrathoracic fluid volumes if the MR persists. Having the ability to detect an immediate increase in LAP with an implantable LAP sensor offers an advantage for earlier intervention in comparison with a CRT-D device that has the potential to detect via admittance measurements a subsequent rise in intracardiac and intrathoracic fluid volumes.

LAP estimation

Despite the presence of a hysteresis-type pattern on the correlation plots between admittance and LAP, the present study also demonstrates that a relatively accurate estimate of LAP may be derived from intrathoracic impedance (A_{LAP}) with use of a linear model. Bland–Altman plots of the difference between A_{LAP} and direct LAP measurements shows that, for all six vectors, there was a relatively good agreement between LAP values measured by the two methods. Bland–Altman analysis determined that 95 % confidence limits for the mean difference between the two methods (2 S.D.) for all six vectors were in the range of 8.3–10.3 mmHg, which, of note, is in a similar range for the accuracy reported for other implantable haemodynamic monitors [19,20]. Hence, A_{LAP}, even when using a linear model, provides a good estimate of LAP that may be clinically useful in providing an early warning of HF deterioration.

Limitations

As seen in the present study, one limitation of the intrathoracic impedance measurements derived from a CRT-D device is that a variable amount of time is required for the impedance signals to stabilize during the system maturation period after implantation. In addition, shifts in intrathoracic impedance measurements may also transpire in response to changes occurring at the electrode/tissue interface and/or as a consequence of a mechanical failure of the implanted lead. Intrathoracic impedance measurements are also prone to change as a result of non-cardiac events, such as pneumonia, pleural effusion, pneumothorax and device pocket infection. Impedance measurements potentially may become more reliable when a longer period of time is allocated for system maturation and when utilizing vectors that employ the LV_{ring} electrode.

Natriuretic peptides

In agreement with previous work using our ovine pacing model of HF [16], the present study demonstrates that plasma concentrations of both ANP and BNP correlate well overall with changes in pacing rate and LAP. Our current data additionally shows an especially strong relationship during the third week of the study when acute alterations in pacing were conducted. During this period, hormone levels fell and rose within the first hour of pacing adjustment (Figure 4), tightly reflecting changes in LAP. This suggests that the natriuretic peptides may be excellent markers of acute changes in LAP as may be seen with acute decompensation to raised pressures or following rapid unloading of filling pressures that would be seen with aggressive diuretic therapy.

Although both ANP and BNP are known to reflect the degree of atrial and ventricular wall stress [11], they both also serve as a compensatory hormonal mechanism during HF and, as demonstrated in the present study, may have a natural tendency to 'overshoot' in response to acute changes in LAP and haemodynamics when rapid ventricular pacing was abruptly changed. Although the reasons for the observed overshoot are unclear, it may reflect the rapid release of both ANP and BNP from storage in atrial granules, resulting in some depletion of stored peptide, followed by a new steady state of production/release in response to changed haemodynamic stimuli over subsequent hours. ANP correlated with LAP across all time points of the study and had a faster response with a shorter-lived overshoot in response to acute changes in pacing in comparison with BNP. Nonetheless, BNP and the N-terminal pro-BNP, in particular, have been advocated for HF monitoring (by virtue of their predominantly ventricular origin and slower clearance rate from plasma), with their potential utility for guiding therapy first reported a decade ago [10]. Our findings indicate that changes in both ANP and BNP appear to be excellent markers of concordant shifts in LAP, particularly under pathophysiological conditions characterized by chronic volume and cardiac overload, and also have an ability to respond rapidly to acute (over hours) rises and falls in LAP.

In contrast with the strong relationship between ANP/BNP and LAP demonstrated in the present study, correlations between filling pressures and plasma BNP levels observed in the ICU (intensive care unit) setting have been modest at best [21]. There are a number of

differences between our study and those set in the ICU, where investigations performed in the latter have been largely cross-sectional, and observations made at one or two time points in small- to moderate-size cohorts of subjects with advanced cardiac dysfunction. Subjects in these studies generally exhibited filling pressures that were either high normal or elevated, and few or no subjects had normal or low filling pressures. In the experimental model described in the current study, however, multiple time points were examined under a variety of conditions associated with filling pressures across a wide range from normal to severely elevated. In addition, in this model, there was no confounding from other factors such as diuretic or vasodilator therapy to complicate the relationship between the natriuretic peptides and LAP.

Conclusions

In conclusion, the present study assessed head-to-head comparisons of direct LAP measurements with multivector intrathoracic impedance and plasma natriuretic peptide levels. All three strategies generally track onset and recovery from HF. LAP has the required accuracy and response pattern to acute physiological changes that make it a suitable parameter for dynamically adjusting daily prescriptions in ambulatory HF patients based on a physician-directed patient self-management therapeutic paradigm. Intrathoracic impedance may be utilized to derive estimates of LAP and to detect trends that may be indicative of a change in clinical status. However, because of the inability of intrathoracic impedance measurements to acutely track rapid physiological changes and limited specificity, A_{LAP} may not be an optimal parameter for dynamically adjusting daily prescriptions. Natriuretic peptides closely track acute alterations in LAP and may be utilized for guiding HF therapy, but because the current assay technology requires a visit to the clinic, natriuretic peptides cannot be used for altering daily prescriptions using a physician-directed patient self-management therapeutic paradigm. All three strategies show promise for improved monitoring of HF and early detection of decompensation, either alone or in combination.

AUTHOR CONTRIBUTION

Miriam Rademaker was in charge of the conception/design, data acquisition/analysis, statistical analysis and manuscript generation. Christopher Charles was responsible for the research conception/design, data analysis, statistical analysis and manuscript generation. Iain Melton was in charge of the research conception/design, surgical instrumentation and pre-submission manuscript review. Mark Richards was responsible for the research design and pre-submission manuscript review. Christopher Frampton undertook the statistical analysis. Jeff Siou and Fujian Qu were responsible for data acquisition/analysis. Neal Eigler and Richard Troughton were in charge of the research conception/design and pre-submission manuscript review. Dan Gutfinger was also responsible for the research conception/design and manuscript generation.

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