Background: Central venous pressure (CVP) is measured to assess intravascular fluid status. Although the clinical gold standard for evaluating CVP is invasive measurement using catheterization, the use of catheterization is limited in a clinical setting because of its invasiveness. We developed novel non-invasive technique, enclosed-zone (ezCVP™) measurement for estimating CVP. The purpose of this study was to assess the feasibility of ezCVP and the relationship between ezCVP and CVP measured by a catheter.

Methods and Results: We conducted 291 measurements in 97 patients. Linear regression analysis revealed that ezCVP was significantly correlated with CVP (r=0.65, P<0.0001). The Bland-Altman analysis showed that ezCVP had an underestimation bias of −2.5 mmHg with 95% limits of agreement of −14.1 mmHg and 9.6 mmHg for CVP (P<0.0001). The areas under the curves of receiver operating curve with ezCVP to detect the CVP ≥12 cmH2O (8.8 mmHg) and CVP >10 mmHg were 0.81 or 0.88, respectively. The sensitivity, specificity and positive likelihood ratio of ezCVP for the CVP ≥8.8 mmHg and CVP >10 mmHg were 0.59, 0.96 and 14.8 with a cut-off value of 11.9 and 0.79, 0.97 and 26.3 with a cut-off value of 12.7.

Conclusions: These findings suggest that ezCVP measurement is feasible and useful for assessing CVP.

Key Words: Central venous pressure; ezCVP; Oscillometric method

C

entral venous pressure (CVP) is often measured in clinical practice to assess intravascular fluid status and cardiac preload. Measurement of CVP is particularly valuable for the management of heart failure (HF).1–4 The prognosis for patients with HF whose CVP remains at an elevated level is poor, even if appropriate guideline-directed therapy is provided.5–10 Even after successful decongestion, measurement of CVP is thought to be useful for detecting exacerbation of HF, which can progress the disease severity and result in a poor prognosis.11 Therefore, the measurement of CVP is quite important in the management of HF.

Although the clinical gold standard for evaluating CVP is invasive measurement using right heart catheterization via the central venous cava, the use of heart catheterization is limited in a clinical setting because of its invasiveness. As an alternative, for evaluation of intravascular fluid status, patients can monitor body weight and edema by themselves, and health-care providers can evaluate jugular venous pulsation (JVP), heart sounds and edema. These evaluations play pivotal roles in the management of HF.1–4 However, physical assessment involves some uncertainty due to the patient’s condition and health-care provider’s skill. Echocardiographic assessment of respiratory change of the inferior
artery disease (n=9), valvular heart disease (n=54), cardiomyopathy (n=30) and other diseases (n=4). Exclusion criteria were as follows: persistent atrial fibrillation, use of positive airway pressure in the right-heart catheterization study, inability of the patient to hold his/her breath at end-expiration for measurement of CVP, and inadequacy of cuff placement around the right upper arm. This study was approved by the ethics committee of Hiroshima University (reference number: C20160070). All participants gave written informed consent for participation. This study was conducted in accordance with the Declaration of Helsinki. The individual de-identified participant data will not be available to the public.

Measurement of Central Venous Pressure

Each patient was placed in the supine position on the angiography system. A 5 Fr Swan-Ganz pulmonary catheter (Zeon Medical Inc., Toyama, Japan) was inserted into the right internal jugular vein and connected to a multimodular monitor via a transducer that was zeroed to the level of the mid-axillary line. After measurements for routine hemodynamic assessment including measurements...
Measurement of ezCVP was started immediately after the momanometer pump to control cuff pressure automatically. (PVM-9901, Nihon Kohden. Co.) equipped with a sphygmomanometer pump to control cuff pressure automatically. Figure 2 shows the mid axillary line. A cuff pressure control monitor and transducer that was zeroed to the level of medical staff and was connected to a modified bedside Kohden. Co.) was placed around the right upper arm by and the radial artery sheath, a blood pressure cuff (Nihon prior to insertion of the Swan-Ganz pulmonary catheter measurement of pulmonary artery wedged pressure (PAWP), pulmonary artery pressure (PAP), right ventricular pressure (RVP) and cardiac output, the tip of the catheter was placed in the right atrium to measure right atrial pressure (RAP). RAP was measured at end-expiration with breath-holding for 3 cardiac cycles, and the average of 3 measurements of the mean RAP was used as the mean CVP. A 4 Fr sheath was inserted into the left radial artery for coronary angiography and for measurements of left ventricular pressure and arterial blood pressure.

**Table. Clinical Characteristics and Hemodynamic Status of Participants**

| Variables                                         | n=97       |
|---------------------------------------------------|------------|
| Age, years                                        | 68.5±15.4  |
| Female, n (%)                                     | 33 (42.9)  |
| Height, m                                         | 158.7±11.4 |
| Body weight, kg                                   | 59.8±11.9  |
| Body mass index, kg/m²                            | 23.7±3.6   |
| Coronary artery disease, n (%)                    | 9 (9.3)    |
| Valvular heart disease, n (%)                     | 54 (55.7)  |
| Cardiomyopathy, n (%)                             | 30 (30.9)  |
| Others, n (%)                                     | 4 (4.1)    |
| Hypertension, n (%)                               | 58 (75.3)  |
| Diabetes mellitus, n (%)                          | 51 (66.2)  |
| Dyslipidemia, n (%)                               | 42 (54.5)  |
| Diuretics, n (%)                                  | 32 (41.6)  |
| Renin angiotensin system inhibitor, n (%)         | 39 (51.7)  |
| β-blocker, n (%)                                  | 30 (39.0)  |
| Calcium channel blocker, n (%)                    | 28 (36.4)  |
| Left ventricular ejection fraction, %             | 52.9±16.5  |
| Severe tricuspid regurgitation, n (%)             | 7 (8.6)    |
| Hemoglobin, g/dL                                  | 12.8±2.3   |
| Creatinine, mg/dL                                 | 0.9 (0.7–1.3) |
| N-terminal pro-brain natriuretic peptide, pg/mL   | 16.0<27.0  |
| Heart rate, beats/min                             | 71.9±12.0  |
| Systolic blood pressure, mmHg                     | 129.5±20.5 |
| Diastolic blood pressure, mmHg                    | 74.2±14.3  |
| Cardiac index, L/min/m²                            | 2.8±0.9    |
| Right atrial pressure, mmHg                       | 8.0 (6.0–10.0) |
| Systolic pulmonary artery pressure, mmHg          | 31.7±10.2  |
| Diastolic pulmonary artery pressure, mmHg         | 16.4±6.1  |
| Mean pulmonary artery pressure, mmHg              | 22.8±8.0   |
| Mean pulmonary artery wedge pressure, mmHg        | 14.7±6.5   |

Results were presented as mean±standard deviation for continuous variables with normal distribution or median (interquartile range) for continuous variables with non-parametric distribution.
Relationship Between CVP and ezCVP

Of the total of 234 measurements, ezCVP could be declared in 187 measurements (81.0%) and could not be declared in 47 measurements due to noises being mixed into ezCVP. Therefore, we excluded those 47 measurements from analysis to assess the relationship between CVP and ezCVP. Figure 3 shows a scatter plot for ezCVP vs. CVP among the remaining 187 measurements. Linear regression analysis revealed that ezCVP correlated with CVP (r=0.65, P<0.0001). Lin’s ρc was 0.53 and indicated poor agreement between CVP and ezCVP (Figure 3).

Of the 78 patients, ezCVP was declared in all of the 3 measurements in 47 patients (60.2%), in 2 of the 3 measurements in 16 patients (20.5%), in 1 of the 3 measurements in 14 patients (17.9%), and in none of the 3 measurements in 1 patient (1.2%).

When CVP is <5 mmHg, it is below the threshold for ezCVP to quantify CVP. Therefore, to validate the quantitative ability of ezCVP, Bland-Altman analysis between ezCVP and CVP was performed for 63 measurements with CVP of ≥5 mmHg. ezCVP had an underestimation bias of −2.5 mmHg, with 95% limits of agreement of −14.1 mmHg and 9.6 mmHg for CVP (P<0.0001) (Figure 4). The linear regression analysis demonstrated that the difference between CVP and ezCVP significantly correlated with the average in ezCVP and CVP (Figure 4, blue line).

In 108 of the 187 measurements with a 0 reported by ezCVP, CVP was <5 mmHg in 48 measurements.

Detection of Abnormal Elevation of CVP

Figure 5A and 5B show ROC curves of ezCVP to discriminate CVP ≥12 cmH2O (8.8 mmHg) and CVP >10 mmHg. The AUC values of ROC curves with ezCVP to detect CVP ≥12 cmH2O (8.8 mmHg) and CVP >10 mmHg were 0.81 and 0.88, respectively. The sensitivity, specificity and positive likelihood ratio (LR+) of ezCVP for CVP ≥8.8 mmHg and CVP >10 mmHg were 0.59, 0.96 and 14.8 with a cut-off value of 11.9, and it was 0.79, 0.97 and 26.3 with a cut-off value of 12.7, respectively.

Discussion

This is the first report about the feasibility and validity of ezCVP measurement. The major findings of this study
were as follows: (1) the feasibility of ezCVP measurement was acceptable as an initial attempt; (2) ezCVP significantly correlated with CVP; and (3) the ability of ezCVP to detect abnormal elevation of CVP was good, with high specificity and high LR+.

**Principle of Venous Pressure Measurement by the Oscillometric Method**

In the present study, we demonstrated that the oscillometric method was applicable for the measurement of venous pressure in the upper arm. We applied the same principle of the oscillometric method used in the measurement of arterial blood pressure to the measurement of venous pressure. In the measurement of arterial pressure by the oscillometric method, the highest amplitude of cuff pressure oscillation is documented when cuff pressure is equal to the mean arterial pressure. It is presumed that the same phenomenon occurs in the measurement of venous pressure; that is, ezCVP seems to be able to reflect mean venous pressure of the upper arm. In the present study, we confirmed that it is possible to measure the change of venous volume caused by venous pressure variation using the pressure cuff. By the measurement principle, ezCVP should be a multiple of 5 between 40 mmHg and 5 mmHg. However, due to the performance of the sphygmomanometer pump and the control algorithm, it was difficult to make the cuff pressure a multiple of 5 strictly. Therefore, the ezCVP took a value other than a multiple of 5 and formed a similar distribution to a continuous distribution.

**Feasibility of the ezCVP Measurement**

In the present study, ezCVP could be declared in 187 of the 234 measurements (81.0%) and in all but one of the 78 patients. Body motion, deep respiration and/or arrhythmia during the measurement were thought to be causes of noise mixed into ezCVP. The results are acceptable as an initial attempt, but the current system has room for improvement for clinical use.

**Relationship Between ezCVP and CVP**

In the present study, we demonstrated that ezCVP was significantly correlated with CVP, with significant underestimation bias. Lin’s coefficient of concordance between CVP and ezCVP was poor. In addition, ezCVP had high specificity, high LR+ and modest sensitivity for detection of elevated CVP. These results were the most important results of the present study. From the viewpoint of clinical implication, the ability to detect elevated CVP is a prerequisite for ezCVP. Health-care providers assess JVP to estimate whether CVP is abnormally high. The LR+ of the JVP examination for detecting CVP of more than 12 cmH₂O was reported to be 10.4. Therefore, in the present study, we tested the ability of ezCVP to detect CVP of more than 12 cmH₂O. The LR+ of ezCVP was better than LR+ of the JVP examination previously reported. We also tested the ability of ezCVP to detect CVP of more than 10 mmHg, which is commonly used in an echocardiographic examination as the cut-off value of elevated CVP. ezCVP was useful for qualitative assessment of CVP; therefore, underestimation bias does not seem to be a serious problem in qualitative assessment of CVP.

In 108 of the 187 measurements with a ezCVP of 0, CVP was <5 mmHg in 48 measurements. In those 108 measurements, CVP of <5 mmHg is considered to have been properly evaluated by ezCVP. However, accurate measurement of CVP <5 mmHg is not possible theoretically by current ezCVP because cuff pressure was decreased automatically from 40 mmHg to 5 mmHg by a 5-mmHg step. The improvement of cuff-pressure control algorithm and the validation study are needed to measure CVP <5 mmHg.

The cuff pressure for measuring ezCVP was set to reduce the pressure by 5 mmHg, and ezCVP showed various values other than multiples of 5 because it was difficult to strictly reduce cuff pressure by 5 mmHg in each step.

**Clinical Perspectives**

Self-monitoring of body weight by patients with HF is recommended in the guidelines of HF because monitoring body weight is easy for anyone to do to assess body fluid status and prevent further exacerbation of HF. In contrast, in some patients with advanced HF, body weight gradually decreases as a result of malnutrition and cardiac
ezCVP cachexia. In those patients, change of body weight cannot be an appropriate indicator of intravascular fluid status. Estimation of CVP plays an important role in the management of body fluid in such cases. Evaluation of JVP can also provide useful information, though it requires expertise. However, ezCVP measurement can allow inexperienced health-care providers to assess CVP.

Study Limitations
There are a number of limitations in this study. First, we excluded patients with atrial fibrillation, which is the most common arrhythmia in HF. We assumed that ezCVP could not be measured accurately in patients with atrial fibrillation. The oscillometric method is potentially inappropriate in patients with atrial fibrillation because CVP fluctuates due to a lack of atrial contraction and an irregular ventricular rhythm. Second, patients were placed in the supine position on the angiography system and medical staff placed the cuff. In the future, ezCVP measurement should be adapted for monitoring CHF status at home.

Conclusions
In conclusion, we demonstrated that a novel method named ezCVP measurement was feasible and useful for assessing CVP. The results of this study warrant further research and development of this technique for future clinical application.

Funding
This study was funded by Nihon Kohden Co. Ltd.

Disclosures
T.H., Y.S., Y.D., H.S., K.N., K.I., S. Kuriu, Y.F., H.H., S.M., S. Kishimoto, M.K., T.M., C.G., K.N., T.T., and Y.K. have no conflicts of interest to declare. A.N. received grants from TWOCELLS Co. Ltd., MSD K.K., Astellas Pharma Incorporated, and Teijin Pharma Limited, and honoraria from Kyowa Hakko Kirin Co. Ltd. and CHUGAI Pharmaceutical Co. Ltd. K.N. received honoraria and grants from Daiichi Sankyo Co. Ltd. and MSD K.K., and honoraria from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co. Ltd., Mochida Pharmaceutical Co. Ltd., Astellas Pharma Incorporated, Teijin Pharma Limited, and Abbott Japan Co. Ltd. Y.H. received consulting fees from Kyowa Hakko Kirin Corporation related to this study, as well as honoraria and grants from Mitsubishi Tanabe Pharma Corporation, Teijin Pharma Limited, Boehringer Ingelheim GmbH, Merck Sharp & Dohme Corporation, Sanofi K.K., AstraZeneca K.K., Takeda Pharmaceutical Co. Ltd., Astellas Pharma Incorporated, Daiichi Sankyo Co. Ltd., Mochida Pharmaceutical Co. Ltd., Nihon Kohden Corporation, Shimogoi Co. Ltd., Nippon Sigmax Co. Ltd., Sanwa Kagaku Kenkyouho Co. Ltd., Unex Corporation, and Kao Corporation, and honoraria from Radiometer Limited, Omrorn Corporation, Sumitomo Dainippon Pharma Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Torii Pharmaceutical Co. Ltd., Kowa Co. Ltd., Fujifukusin Co. Ltd., Amgen Astellas BioPharma K.K., Nippon Shinyaku Co. Ltd., Iliamr Medical Limited, Bayer Holding Limited, Eli Lilly K.K., and Otsuka Pharmaceutical Co. Ltd. Y.K. received honoraria from Mitsubishi Tanabe Pharma Corporation, Teijin Pharma Limited, Boehringer Ingelheim GmbH, Merck Sharp & Dohme Corporation, Sanofi K.K., AstraZeneca K.K., Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Kowa Co. Ltd., Nippon Shinyaku Co. Ltd., Bayer Holding Limited, and Ono Pharmaceutical Co. Ltd. Both H.M. and T.U. are employees of Nihon Kohden Co. Y.K. is a member of Circulation Journal’s Editorial Team.

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