Pathophysiology and Evaluation of Severity of Congestive Heart Failure on the Basis of Venous Characteristics

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To elucidate the possibility of grading the severity of congestive heart failure by using venous characteristics, we constructed venous pressure-volume curves (PVR) and calculated venous stiffness constants (K). In addition, effects of vasoactive drugs on venous distensibility were studied.

A venous pressure-volume curve could be fit well by an exponential curve \( r = 0.98 \pm 0.01 \). The PVR was shifted to the left with an increase in the clinical severity of congestive heart failure. The exponent of these curves, K, increased as the PVR was shifted to the left. K correlated with heart rate \( r = 0.52, p < 0.01 \), right atrial pressure \( r = 0.54, p < 0.02 \) and mean pulmonary arterial pressure \( r = 0.47, p < 0.04 \). Nitroglycerin and amrinone dilated veins and decreased K by 19.6 \( \pm \) 6.9% \( p < 0.03 \) and 14.0 \( \pm \) 4.3% \( p < 0.02 \), respectively. Changes in K \((\Delta K)\) during the nitroglycerin and amrinone infusions correlated closely with the baseline K \((\Delta K = -0.41K + 0.22, r = 0.92, p < 0.01)\). Therefore, the venodilating effects of these drugs were greater in patients with more severe congestive heart failure.

The venous stiffness constant could be useful to grade the severity of congestive heart failure.

New York Heart Association function classes\(^1\) are widely used to express the clinical severity of congestive heart failure. The functional class depends upon subjective symptoms including shortness of breath and dyspnea which are related to pulmonary congestion, sometimes induced by vasoconstriction. Although the precise mechanism is not known, vasomotor tone is elevated in congestive heart failure\(^2\)\(^\text{--}\)\(^5\). Both resistance and capacitance vessels are constricted in congestive heart failure. Initially, the venoconstriction increases cardiac output according to the Frank-Starling mechanism\(^6\) by increasing filling pressure. However, excess vasoconstriction induces pulmonary congestion without increasing cardiac output and leads to a deterioration in congestive heart failure. Accordingly, the degree of vasoconstriction may be different among the levels of severity of congestive heart failure. The purpose of this study is to elucidate the relationship between severity of congestive heart failure and venous characteristics and to evaluate the effects of vasoactive drugs on venous characteristics in congestive heart failure.

**PATIENTS AND METHODS**

The study group was composed of 31 patients aged 32 to 88 years (mean 56.2). The cause of
heart failure were old myocardial infarction in eight patients, dilated cardiomyopathy in 5, aortic regurgitation in 4, mitral stenosis in 3, angina pectoris in 3, mitral stenosis and regurgitation in 2, mitral regurgitation in 2, hypertensive heart disease in 2, hyperthyroidism in 1 and mitral prolapse in 1. Eight patients were in New York Heart Association functional class I (mean age 50.9), 13 in class II (54.4), 6 in class III (61.0) and 4 in class IV (65.5). All medications except digitalis were withheld 12 hours prior to the study. A protocol was approved by the Ethical Committee of the Hospital of the University of Tokyo and informed consent was obtained from each patient.

Venous pressure-volume curves were constructed and venous stiffness constants were calculated as an index of venous characteristics. All studies were carried out with patients in the supine position. Forearm volume changes were measured with a gallium in rubber strain gauge (SPG 16, Medasonic Inc., Mountain View, California) by the venous occlusion technique. The strain gauge was placed 5 cm below the antecubital fossa. A pediatric cuff was placed around the wrist to stop arterial blood flow to the hand. The forearm was elevated so that resting venous pressure was zero. Venous pressure was measured through a 21 gauge tube inserted into a vein and advanced so that its tip lay just distal to the strain gauge. This tube was connected to a pressure transducer (Statham p 50, Gould Inc., California). Signals were amplified by a Fukuda Denshi DS-1000 patient monitor system (Fukuda Denshi LTD., Tokyo) and recorded on a thermal recorder AU-5001 (Fukuda Denshi LTD.) at a paper speed of 5 mm/sec. A venous pressure-volume curve was constructed by plotting changes in forearm volume against venous pressure from 2 to 24 mmHg by 2 mmHg increments. The venous pressure-volume curve was fit to the formula \( VP = Po \times \exp (K \Delta V) \), (VP; venous pressure, Po; intercept of Y-axis, K; venous stiffness constant, \( \Delta V \); change in forearm volume). Four sequential measurements were carried out at each condition for the venous pressure-volume curves. The mean correlation coefficient was 0.98 ± 0.01.

Blood pressure was measured in the contralateral arm directly or with a sphygmomanometer. Right heart catheterization was performed for the measurement of right atrial, pulmonary artery and pulmonary capillary wedge pressures.

All studies were performed in a warm and quiet room in the post absorptive state. After baseline measurements were obtained, each drug was administered as follows and measurements were repeated. 1) Norepinephrine; 150 ng/kg/min was infused intravenously 3 min before measurements. 2) Amrinone; 1 mg/kg was injected intravenously over 5 min followed by a continuous infusion of 5 mcg/kg/min and mea-

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measurements were made 15 min after the initiation of infusion. 3) Nitroglycerin; 5 cm of nitroglycerin ointment was applied 15 min before measurements. 4) Alpha human atrial natriuretic polypeptide; 0.1 μg/kg/min was infused 15 min before measurements. 5) Nilvadipine (a new dihydropyridine derivative Ca\textsuperscript{2+} blocker); 6 mg of powder was administered orally and measurements were made 30 min later.

All data are expressed as mean ± SEM. ANOVA was used for analysis of venous stiffness constant and Student's t-test was used for comparison between two groups. The Wilcoxon sign rank test was employed for the evaluation of changes in venous stiffness constant induced by vasoactive drugs. Relationships between the venous stiffness constant and hemodynamics were evaluated by linear regression analysis. Relationships between ln VP and ΔV were also estimated by linear regression analysis for venous pressure-volume curve. A p value of less than 0.05 was regarded as statistically significant.

**RESULTS**

Venous pressure-volume curves of New York Heart Association functional classes are shown in Fig. 1. The venous pressure-volume curve was shifted to the left with increasing severity of congestive heart failure as defined by the New York Heart Association functional class. The equation for the venous pressure-volume curve in the group with New York Heart Association functional class I or II was VP = 1.30 exp (0.70ΔV), and VP = 1.20 exp (1.77ΔV) in class III or IV. The corresponding venous stiffness constant of each group is shown in Fig. 2. The mean venous stiffness constant (100g tissue/ml) of the group in class I or II was 0.81 ± 0.10, and 2.11 ± 0.34 (mean ± SEM) in class III or IV.

The venous stiffness constant (K) correlated with heart rate (HR) (K = 14.8HR + 59.9, \( r = 0.52, \ p < 0.01 \)), mean right atrial pressure (RAP) (K = 3.1RAP + 0.4, \( r = 0.54, \ p < 0.02 \)) and mean pulmonary arterial pressure (PAP) (K = 5.2PAP + 12.1, \( r = 0.47, \ p < 0.04 \)). There were no statistically significant relationships between the venous stiffness constant and hemodynamic parameters such as arterial blood pressure, cardiac output, pulmonary capillary wedge pressure, systemic vascular resistance, forearm blood flow and forearm vascular resistance.

Effects of vasoactive drugs on venous stiffness are shown in Fig. 3. Norepinephrine increased venous stiffness constant (K) by 40.0 ± 12.0% (\( p < 0.03 \)). Nitroglycerin decreased K by 19.6 ± 6.9% (\( p < 0.04 \)). Aminodone decreased K by 14.0 ± 4.3% (\( p < 0.02 \)). Neither nilvadipine and alpha human natriuretic peptide changed K significantly. Both nitroglycerin and aminodone decreased K. The changes in venous stiffness constant (ΔK) during the nitroglycerin and aminodone infusions correlated closely with the baseline venous stiffness constant (ΔK = −0.41K + 0.22, \( r = 0.92, \ p < 0.01 \)).
DISCUSSION

Practically, forearm and leg veins are the only areas where clinical studies of venous characteristics can be performed in man. In this study venous characteristics in congestive heart failure were studied in the forearm using a plethysmographic technique.

Venous distensibility has been estimated by "venous tone"\textsuperscript{7,8} a venous pressure-volume curve\textsuperscript{9,10} and the change in a forearm volume when an occlusion cuff is inflated to 30 mmHg.\textsuperscript{11} Venous pressure-volume curves have been constructed by the stepwise venous occlusion technique. However, in this study venous pressure volume curves were constructed by plotting venous changes in forearm volume against venous pressures, which were measured simultaneously. A venous pressure-volume curve could be fit closely by an exponential function and thereby venous stiffness constant could be calculated.

Shifts of the venous pressure-volume curve observed were characterized by changes in the calculated venous stiffness constant. This result is consistent with venous distensibility being decreased with increasing severity of congestive heart failure which can be evaluated quantitatively by calculating the venous stiffness constant.

In this study venous stiffness constants correlated with right atrial pressure. Elevation in venous tone shifts the venous return curve to the right and increases right atrial pressure and filling pressure. However, a decrease in right atrial pressure does not necessarily mean venodilatation or a decrease in venous tone, because a decrease in intravascular blood volume also decreases right atrial and filling pressures.\textsuperscript{6}

It has been shown that venous distensibility decreases in patients with congestive heart failure.\textsuperscript{7,7} However, the precise mechanism remains unclear. There are several possibilities. Neurohumoral mechanisms play a major role in decreased venous distensibility in congestive heart failure. Sympathetic nervous tone is elevated and plasma norepinephrine is high in congestive heart failure.\textsuperscript{12} Sympathetic nervous stimulation and plasma norepinephrine induce venoconstriction.\textsuperscript{13,14} In addition phenolamine increases venous distensibility in congestive heart failure.\textsuperscript{15} These facts are consistent with a hypothesis that sympathetic nervous stimulation and plasma norepinephrine constrict veins by stimulating alpha receptors in congestive heart failure. In addition to norepinephrine, angioten
tsion has a hormonal role in venoconstriction.\textsuperscript{16,17} Local factors have some effect in altering venous distensibility.\textsuperscript{18} Edematous venous vessel walls, with increased sodium content, and elevated perivascular tissue pressure may also decrease venous distensibility.\textsuperscript{4}

Alpha human atrial natriuretic polypeptide increases plasma cGMP and induces relaxation of vascular smooth muscle.\textsuperscript{19,20} This peptide has been deduced to dilate veins from decreases in right atrial and filling pressures.\textsuperscript{21,22} On the other hand, several animal studies have shown that alpha human natriuretic peptide increases resistance to venous return and decreases circulatory capacitance.\textsuperscript{24} The result of this study showed that alpha human natriuretic peptide did not dilate constricted forearm veins.

Both nitroglycerin and amrinone dilated constricted veins and decreased venous stiffness constants. The change in venous stiffness constant correlated closely with the baseline venous stiffness constant. This result reveals that effects of venodilating drugs in part depend on degree of venoconstriction. Venodilating effects of these drugs were greater in patients with more severe congestive heart failure.

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