Effects of Injection Site on the Accuracy of Thermal Washout Right Ventricular Ejection Fraction Measurements in Clinical and Model Investigations*

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The purpose of this investigation was to improve the accuracy of measurement of right ventricular ejection fraction (RVEF) using the modified Swan-Ganz catheter. Three serial ejection fractions (EFs) (EF1, 2, 3) and the mean were calculated, based on Holt's theory. RVEFs were compared between right ventricular (RV) and atrial (RA) injection in ten intensive care unit (ICU) patients using a modified catheter having RV and RA orifices (15 cm and 30 cm from the distal end, respectively), and paired or triplicate (eight patients) measurements were performed. To determine what factors interfere with RVEF, a model heart (with diastolic volume of 150 ml) was constructed, in which model injection of cold water to the direct inflow tract (RA), to the direct mixing chamber (RV), or through the catheter running in the inflow tract were compared. When EFs were compared between RV and RA injection, those for the former were greater (RV vs RA in EF1 and EFmean: 0.46±0.15 vs 0.23±0.11 in EF1, and 0.45±0.13 vs 0.28±0.11 in EFmean, mean±SD, p<0.01). When the serial EFs were compared in each injection type, in the RV injection EF3 was the smallest as was EF1 in the RA injection. The same phenomenon was observed in the model as in the patients, and moreover when cold water was injected in RA through a catheter running through the circuit, EFs were greatly underestimated (EF1=0.29±0.02 at preset EF=0.4). We conclude that these phenomena were caused by sluggish movement of the cold indicator from RA to RV when injected into RA, and by interference with the cooled cardiac chamber and catheter. Consequently, the first or second EFs obtained from RV injection might be closest to the actual values because of the least interference with those factors. (Chest 1991; 99:436-43)

For better understanding of right ventricular (RV) physiology, the indicator washout method for measurement of right ventricular ejection fraction (RVEF) has been developed because of RV anatomic characteristics.1 Fundamental investigations into the indicator washout method have been made in humans, animals, and artificial models using dye, electrical conductivity, and thermal washout methods,2-5 and the newly developed pulmonary arterial catheter equipped with a rapid response thermistor makes RVEF available for clinical investigation.6 A new algorithm for calculation of RVEF has been developed, based on the theory that the downslope of a thermal washout curve obtained after injecting cold water just above the tricuspid valve to attain good mixing in the right ventricle can be fitted to a single first-order exponential curve,6,11 and this method has been used clinically.12-18 However, several important questions remain to be answered; whether the downslope of a thermal washout curve can be fitted to a single exponential curve and at what part (that is, the whole downslope or part of the downslope), whether successive ejection fractions (EFs) in a thermal washout curve are always the same, and whether the right atrial (RA) injection of cold water makes measurement of RVEF more accurate than does RV injection. The purpose of this study is to answer these questions. Serially measured EFs between RA or RV injections in the same patient were compared and the same procedure was repeated in a model heart. We determined that the serially measured EFs were different from each other (namely they did not fit a single exponential curve), the EFs obtained from RA injection were lower than those from RV injection, and that the recommended injection site was RV. Moreover, it was concluded that the first and/or second calculated EFs in a thermal washout curve obtained from RV injection might be closest to the actual values, and that catheter cooling affected the results considerably.

METHODS AND MATERIALS

Patient Population

Ten patients treated in the general intensive care unit (ICU) of

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Gunma University Hospital were examined in the investigation (from January 1, 1989 to May 31, 1989) with permission given by the patients themselves (if possible) or their closest relatives and allowance of the ethical committee of the Gunma University Hospital. Mean patient age was 61 ± 13 years (range, 41 to 83 years). Nine patients were male and one was female. Three cases were of ruptured aortic aneurysm, two involved cardiac surgery, two were of acute respiratory failure, and the three remaining cases involved bacterial pneumonia, massive burn, and hemorrhagic shock, respectively. All patients could breathe for themselves but were hypoxemic (hypocapnic or normocapnic hypoxemia). They therefore were treated with minimal continuous positive airway pressure (CPAP) (less than 10 cm H2O, no mechanical ventilatory support) to maintain arterial oxygen saturation above 90 percent with inspiratory oxygen fraction less than 0.5 using a home-made CPAP system or respirators (Bear 5 ventilator, Bear Medical Systems, Inc., Riverside CA or 7200A Ventilator, Puritan Bennett Corporation, Los Angeles, Ca).18

Analogue of the Cardiac Ventricle

Basic Structure of the Model Heart: A model heart with end-diastolic volume of 150 ml was constructed, the bottom of which was made of a movable rubber board connected to a piston and an electric motor, and the top of which was equipped with two one-way valves (Fig 1). Each valve was connected to the inflow (venous) or outflow (arterial) circuits, which in turn were connected to a large-volume constant-temperature (37°C) reservoir. Warm water from this reservoir filled the chamber and circuits and was circulated by strokes of the artificial heart.

Valvular Structure and Flow Characteristics: One end of a hollow cylinder (internal diameter, 25 mm; height, 35 mm) was covered with a board having a center hole (12-mm in diameter), and the other end with a porous board (six 6.3-mm-diameter circles set in a circle). In this cylinder, a ball (diameter, 22 mm) made of hard nylon occluded the 12-mm hole by compression by a supporting wire spring of pyramid shape (the lower end of the spring [diameter, 6 mm] was secured to the porous end of the cylinder; the upper end was 19 mm in diameter). The spring constant of this spring was 0.025 kg/mm and sufficient to respond to the pressure change generated by the piston movement and to prevent regurgitation. A pair of valves was set at the top of the chamber in opposite directions to each other; one was connected to the inflow (venous) circuit and the other to the outflow (arterial) circuit, and thereby flow was permitted in only one direction, from venous to arterial side. When a bolus of blue dye was injected in the inflow tract, it flowed turbulently into the chamber with movement of the piston, mixed completely and instantaneously in the chamber, and no regurgitation was noted.

Materials Used and Their Thermal Characteristics: The chamber was made from a hard, transparent acrylic resin cylinder, its bottom of a hard rubber, the circuits from transparent polyvinyl chloride hoses, the ball valve from hard vinyl, and the spring from wire. The thermal conductivity of these materials was (0.0005 to 0.0006) (Watts)/(m)·(°C)·1 except for the wire spring (mass of the spring was almost negligible compared with the other parts). Tissues have values of specific thermal conductivities near that of water, although they may be influenced by perfusion condition (Ref. specific thermal conductivity of silver is 1.16, of glass 0.0028, of water 0.0014, of fat 0.0005, and of muscle 0.0011). The model heart thereby had good heat-insulating characteristics comparable to those of tissues and organs.

Injection Ports, Swan-Ganz Catheters, and Records of Thermal Washout Curves: Two separate injection ports were constructed 3 cm below and above the inflow valve, respectively, at which three-way valves prevented leakage and allowed direct injection of cold water into the chamber and the venous circuit. A Swan-Ganz catheter (73R9067, 7 French size, Electro-Catheter Corp. Rahway, NJ) was passed through the venous circuit and its tip was placed
just above the inflow valve, forming another injection port. Another Swan-Ganz catheter, the tip of which was outside the circuit from another port 5 cm above the inflow valve, was placed separately in the venous circuit to detect the influence of catheter cooling on EFs. A rapid response thermistor (identical to that used in the venous circuit) was placed 5 cm above the outflow valve, temperature changes were analyzed by cardiac output computer (identical to that used for measurement in patient), and a thermal washout curve was recorded on a thermal array recorder (WS-641C, NihonKohden, Tokyo, Japan) at a paper speed of 25 mm/s.

Functional Characteristics of the Pump: The stroke frequency of the pump could be varied from 0 to 100 per minute, and the EF was from 0.3 to 0.65. The volume of water displaced by the piston pump (ventricular stroke volume) could be adjusted to any value between 45 and 90 ml by changing the eccentricity of the plunger attachment on a rotating wheel, and it was calibrated by direct measurement of the ejected volume in the cylinder. The volume of the chamber was determined by measuring the water content at diastolic phase and the EF was calculated. Due to the relatively small diameter of the circuit (internal diameter, 20 mm), outflow resistance of the chamber was apparent; however, the power of the motor was sufficient to eject stroke volume forcefully, and no regurgitation or leakage was observed.

Measurement Principles

We adopted the thermal washout technique of Holt for the measurement of right ventricular end diastolic volume (RVEDV) and RVEF. When the cold water was injected into the RV or RA, the thermal washout curve of RV could be obtained for the pulmonary artery with the aid of the rapid response thermistor shown in Figure 2. Four successive end-diastolic plateaus were detected and the three serial EFs were calculated (EF1, EF2, and EF3), as well as EFmean (mean of three EFs) (Fig 2). Clinically, end-diastolic plateaus in the thermal washout curve were determined by the method described previously, briefly outlined as follows: the radial arterial pressure wave, the electrocardiogram, and the thermal washout curve were recorded simultaneously on a microcomputer (PC3801, NEC, Tokyo, Japan) via a commercially available AD converter, and the four successive end-diastolic plateaus were determined by calculating the mean values of the thermal change recorded every 20 ms between the end of QRS and the start of the rapid deflection of arterial systolic wave, starting with the first R-wave occurring after the peak deviation on the thermocouple curve. Three successive EFs were calculated within the residual temperature change of more than 20 percent of peak one and displayed on a monitor together with the thermal washout curve, the determined points of end-diastolic plateaus, electrocardiogram, and arterial pressure wave. If any arrhythmia and/or any distorted thermal curves were noted, the data were abandoned. In the model experiment, end-diastolic plateaus in the washout curve were easily determined as the gradual downslope just before rapid temperature change induced by the subsequent stroke, and the mean points of the gradual downslope were adopted as end-diastolic plateaus. Thus, we did not adopt any time derivative of the curve or signals from the artificial heart showing the start of upward movement of the piston.

Measurement Techniques

Patients: A modified Swan-Ganz catheter (73R90675, 7.5 French size, Electro-Catheter Corp. Rahway, NJ), which was equipped with three lumens (one connected to the distal end, the second to a side hole 15 cm from the tip, and the third to a side hole 30 cm from the tip), and also a rapid response thermistor (90 percent response time being about 100 ms) was inserted into a pulmonary artery through the internal jugular vein. The position of the catheter was confirmed by recordings of characteristic pressure wave of each of the pulmonary arteries (distal end of the catheter), RV (side hole 15 cm from the distal end), and RA (side hole 30 cm from the distal end). Five milliliters of 5 percent dextrose solution in iced water was injected into RA or RV, and the temperature change was analyzed by cardiac output (CO) computer (AH611V, NihonKohden, Tokyo, Japan). The temperature of the injectate in iced water was monitored with a thermistor and used for calculation of CO by the computer. Duplicate or triplicate paired injection in the RA and RV were repeated irrespective of respiratory cycle, and four or six values were obtained at a time. Variation of the measurement in each patient was evaluated using the coefficient of variation, which was obtained by dividing the standard deviation by the mean value and multiplying by 100.

The Model Heart: Different combinations of mechanically preset EFs (0.4, 0.44, and 0.62), stroke frequencies (60 and 100 strokes/min), and injection sites (inflow circuit, chamber, and inflow circuit via the Swan-Ganz catheter) were examined (Table 1). The EFs and the stroke rate were preset at 0.4 or 0.62, and 60 stroke/min, respectively (preset stroke volume and CO were 60 ml or 93 ml, and 3.6 L/min or 5.6 L/min, respectively) and 10 ml of iced water was injected through the Swan-Ganz catheter into the thoracic aorta through the distal end of the catheter. The stroke volume was measured by the drop of CO output which was calculated by the method described above. The stroke volume was recorded by a temperature sensor (WS-641C, NihonKohden, Tokyo, Japan) at a paper speed of 25 mm/s.

Table 1—Experimental Protocol in the Model Heart*

<table>
<thead>
<tr>
<th>EF</th>
<th>Stroke Frequency</th>
<th>Injection Site of Cold Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>60</td>
<td>RA (direct injection)</td>
</tr>
<tr>
<td>0.44</td>
<td>60</td>
<td>RA through Swan-Ganz catheter</td>
</tr>
<tr>
<td>0.62</td>
<td>60</td>
<td>RA (direct injection)</td>
</tr>
<tr>
<td>0.62</td>
<td>100</td>
<td>RA through Swan-Ganz catheter</td>
</tr>
</tbody>
</table>

*RA = right atrium: inflow circuit to chamber 3 cm above inflow valve. RV = right ventricle: chamber.
Table 2—Comparison of Serial Ejection Fractions (EF), Cardiac Output (CO), and Coefficients of Variation, and Correlations of 28 Paired Data Obtained from Injections to RA and RV in Ten Patients

<table>
<thead>
<tr>
<th></th>
<th>EF1</th>
<th>EF2</th>
<th>EF3</th>
<th>EFmean</th>
<th>CO(L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Serial EF and CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA injection</td>
<td>0.23 ± 0.11†</td>
<td>0.30 ± 0.12†</td>
<td>0.31 ± 0.14†</td>
<td>0.28 ± 0.11†</td>
<td>8.18 ± 2.69</td>
</tr>
<tr>
<td>RV injection</td>
<td>0.45 ± 0.15</td>
<td>0.47 ± 0.14</td>
<td>0.39 ± 0.15</td>
<td>0.45 ± 0.13</td>
<td>9.17 ± 4.50</td>
</tr>
<tr>
<td>b. Coefficient of Variation (%) of EFs and CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA injection</td>
<td>22.1 ± 14.3‡</td>
<td>18.0 ± 14.4</td>
<td>16.9 ± 11.4</td>
<td>12.1 ± 6.2</td>
<td>8.0 ± 4.6</td>
</tr>
<tr>
<td>RV injection</td>
<td>7.7 ± 8.7</td>
<td>15.3 ± 7.5</td>
<td>18.6 ± 18.0</td>
<td>8.3 ± 5.3</td>
<td>11.7 ± 6.9</td>
</tr>
<tr>
<td>c. The correlations of the serial EFs and CO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearman's coefficient of correlation</td>
<td>0.422‡</td>
<td>0.341‡</td>
<td>0.520‡</td>
<td>0.504†</td>
<td>0.769‡</td>
</tr>
<tr>
<td>A in (Y = A + BX)</td>
<td>0.052</td>
<td>0.073</td>
<td>0.076</td>
<td>0.004</td>
<td>3.90</td>
</tr>
<tr>
<td>B in (Y = A + BX)</td>
<td>0.375</td>
<td>0.475</td>
<td>0.592</td>
<td>0.623</td>
<td>0.465</td>
</tr>
</tbody>
</table>

*Y = A + BX: (RA injection) = A + B (RV injection). Regression equations were determined by the least square analysis. †p < 0.01, ‡p < 0.05, compared with RV injection (in a and b), and level of significance of coefficient of correlation (in c), §p < 0.01, ¶p < 0.05, compared with EF1 (in a and b).

was injected directly into the chamber or the inflow tract under each condition. These particular EFs were chosen as representing a relatively high level and a low level in the situation of limited performance of the artificial heart. Cold water was subsequently injected into the inflow tract via the Swan-Ganz catheter passed through the venous circuit (90 cm in length), and the effect of catheter cooling was observed. To determine the influence of change in heart rate, the stroke rate was increased to 100/min and EF was set at 0.44 (preset stroke volume and CO were 66 ml and 6.6 L/min, respectively) and the same procedure was repeated.

Statistical Analysis

Successive EFs were compared with repeated-measures analysis of variance and when a statistically significant difference was found to exist, further analysis was performed with the Student-Newman-Keuls test for multiple comparisons. One-way analysis of variance for comparison of unpaired data from the three groups, Mann-Whitney test for comparison of unpaired data from two groups, and Wilcoxon's signed rank test for comparison of paired data from two groups were used. A p value less than 0.05 in two-tailed analysis was considered to be significant. All values were expressed as mean ± standard deviation.

RESULTS

Measurement in Patients

A total of 28 paired values were obtained in the ten patients. Duplicate paired measurement was performed in two patients and in the others triplicate paired measurement was undertaken. In comparison of serial EFs in RA or RV injection, EF1 was found to be the lowest in RA injection; however, in RV injection EF1 and EF2 were the same and EF3 was the lowest (Table 2, a). In comparison between RA and RV injections, all EFs were significantly higher in RV injection (Table 2, a). In comparing variation of measurement in each patient between RA and RV injections, the coefficient variation of EF1 in RA injection was significantly higher than that of EF1 in RV injection (Table 2, b). In evaluating correlation of EFs between RA and RV injections, weak correlation only was found (p < 0.05 in EF1 and EF2) (Table 2, c). COs were the same in both RV and RA injection, and their coefficients of variation were close to 10 percent (Table 2, a and b), showing reasonable variation in thermo-dilution CO.

Effect of Different Injection Sites in the Model Heart

In comparing EFs between inflow tract (RA) and chamber (RV) injections, lower EFs in RA injection were recorded in every condition of the pump investigated (Table 3). With injection of cold water through a Swan-Ganz catheter extending 90 cm through the venous circuit, with its tip positioned in RA, the EFs were strikingly lower than preset values (Table 3). Unfortunately, the valve in this heart model was not satisfactorily efficient in preventing regurgitation when the catheter was passed through it into RV, and consequently, we abandoned cold water injection through the Swan-Ganz catheter into RV.

Correlation between the Three Successive EFs in the Model Heart

Less variation in the three successive EFs was apparent in EFs obtained with the low preset EF values of 0.4 or 0.44; however, a successive decrease

Table 3—Comparison of Measured Ejection Fractions in the Model Heart According to Mode of Injection and Pump Conditions

<table>
<thead>
<tr>
<th></th>
<th>EF1</th>
<th>EF2</th>
<th>EF3</th>
<th>EFmean</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (pump conditions: EF = 0.40, Rate = 60 strokes/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/Bolus</td>
<td>0.32 ± 0.03†</td>
<td>0.36 ± 0.02†</td>
<td>0.34 ± 0.01†</td>
<td>0.34 ± 0.01†</td>
</tr>
<tr>
<td>RA/90 cm</td>
<td>0.29 ± 0.02†</td>
<td>0.28 ± 0.03‡</td>
<td>0.28 ± 0.02†</td>
<td>0.29 ± 0.01†</td>
</tr>
<tr>
<td>RV/Bolus</td>
<td>0.39 ± 0.03</td>
<td>0.40 ± 0.02</td>
<td>0.39 ± 0.03</td>
<td>0.40 ± 0.01</td>
</tr>
<tr>
<td>B (pump conditions: EF = 0.62, Rate = 60 strokes/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/Bolus</td>
<td>0.53 ± 0.01†</td>
<td>0.52 ± 0.02†</td>
<td>0.45 ± 0.02†</td>
<td>0.50 ± 0.01§</td>
</tr>
<tr>
<td>RA/90 cm</td>
<td>0.45 ± 0.02†</td>
<td>0.43 ± 0.03§</td>
<td>0.33 ± 0.03†</td>
<td>0.40 ± 0.02†</td>
</tr>
<tr>
<td>RV/Bolus</td>
<td>0.65 ± 0.01</td>
<td>0.50 ± 0.02‡</td>
<td>0.50 ± 0.03‡</td>
<td>0.55 ± 0.02‡</td>
</tr>
<tr>
<td>C (pump conditions: EF = 0.44, Rate = 100 strokes/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA/Bolus</td>
<td>0.38 ± 0.02†</td>
<td>0.40 ± 0.04</td>
<td>0.37 ± 0.03</td>
<td>0.39 ± 0.01†</td>
</tr>
<tr>
<td>RV/Bolus</td>
<td>0.44 ± 0.03</td>
<td>0.43 ± 0.03</td>
<td>0.38 ± 0.04‡</td>
<td>0.42 ± 0.02</td>
</tr>
</tbody>
</table>

*Each value represents mean ± SD of seven values except for RA/ Bolus of B-group (five values). RA/Bolus, RV/Bolus, and RA/90 cm: direct atrial injection, ventricular injection, and injection via 90- cm-long catheter in the inflow circuit, respectively. †p < 0.01, ‡p < 0.05, compared with RV/Bolus. §p < 0.01, ¶p < 0.05, compared with EF1.
which was compatible with the descending side of the thermal washout curve (Fig 4; catheter cooling only). When this temperature change induced by catheter cooling was subtracted from the thermal change obtained by atrial injection via Swan-Ganz catheter, and the EF calculated, the obtained EF was the same as that from the direct atrial injection (Fig 4; corrected values). The corrected EF was 82±4 percent of the preset value (mean ± SD of seven measurements).

**DISCUSSION**

The successive EFs obtained in a washout curve are naturally fluctuating because successive stroke volumes and EFs vary in an actual heart unlike the situation in a mechanical analogue, and hence we consider that calculation of the mean EF from a few successive EFs is reasonable. However, if there were any significant relationships between successive EFs, these would not be caused by physiologic fluctuations, but by artifacts possibly derived from the measurement technique itself. We determined in this experiment that successive EFs were different; moreover,

from EF1 to EF3 was characteristic of EFs obtained with the preset EF value of 0.62 (Table 3). The regression equations for EFs were calculated for the chamber and inflow tract injections, respectively, and showed good linear correlation within the range investigated (preset EF = 0.4 to 0.62) (Fig 3). EF1 or EF2 obtained in the direct chamber injection was closest to the preset EF values and inflow tract injection resulted in underestimation (Fig 3).

**Influence of Catheter Cooling without Injection in the Model Heart**

A Swan-Ganz catheter was installed in the same way as outlined above, except that its tip was placed outside of the circuit, and the injected cold water passed through the circuit without mixing with warm water in the circuit (Fig 1). When the cold water was injected through this catheter, a low-gradient temperature change was detected in the arterial circuit,
the patterns of difference were not the same between EFs obtained from ventricular injection and those from atrial injection. These findings were also seen in the artificial heart. Another finding was that EFs obtained from ventricular injection were larger than those from atrial injection, and the choice of injection site was a critical issue in this method.

Why Did the Serial EFs Differ?

Theoretically, the serial EFs in a washout curve should be the same, and as far as we know, most investigators are calculating the mean value from a few EFs or are considering that the sequence of temperature steps produced by progressive dilution of the indicator is a simple exponential function of time.10,11 However, by analyzing thermal washout curves obtained in patients, we observed that successive EFs increased in RA injection and that EF3 was small in RV injection. A similar phenomenon was observed in the model experiment when the indicator was injected just above the inflow valve (above the tricuspid valve); EF2 was the largest and closest to the mechanically predetermined value. When injection into the chamber (ventricle) was performed directly, EF1 or EF2 was the largest and closest to the mechanically predetermined value and the successive decrease was apparent with a preset EF/stroke of 0.62/60 (Table 3). With a preset EF of 0.62, the residual cold energy in the chamber after the first and second injections was small. A small temperature change could be possibly affected by the cooled chamber, and thereby the resultant temperature change might be falsely exaggerated and EFs would be successively underestimated. However, this phenomenon could not be detected in EFs of 0.40 and 0.44, in either of the inflow circuit or chamber injections, possibly because the residual temperature change may have been relatively large compared with the small temperature change caused by potential cooling of the chamber wall. This may be the reason why this phenomenon has been overlooked by researchers. Salgado and Galletti9 verified the reliability of thermal EF in an artificial heart composed of a rubber balloon enclosed in a glass container connected to a piston pump, and in their figures we find out no evidence of successively changing EFs because the EF is set at less than 0.4. In the inflow circuit injection, the cold indicator could not move to the chamber within a single stroke but required a few strokes (we confirmed that dye injected into the inflow circuit required a few strokes to clear). Consequently, smaller and more stable EFs were recorded in inflow circuit injection than in direct chamber injection; however, EF3 in the case of preset EF of 0.62 in inflow circuit injection was significantly lower than EF1 and EF2, since the residual energy change was so small and may have been possibly affected by cooling of the chamber.

What Was the Effect of Injection Site on EF?

Preference of the RA as an injection site is based on the fact that EFs in dogs after RV injection are less reproducible than those after RA injection, probably a result of inadequate mixing during RV injection.23 This assumption cannot be accepted because the mixing of any indicator within the ventricle is dependent on mixing of the stroke volume entering from the atrium with the residual volume in the ventricle and independent of injection site. In relation to these considerations, Rapaport24 proposes that it is probably useless to inject the indicator into the atrium near the atrioventricular valve in an attempt to obtain better mixing, and on the other hand, atrial injection can cause inaccuracy in the measurement of residual fraction and therefore end-diastolic volume. Our results indicated that the EFs obtained from atrial injection might be more reproducible, but this does not mean these reflected true RVEFs. We suppose that the lower reproducibility in EFs obtained by ventricular injection may be caused by variation in EF values calculated from the latter part of a single thermal washout curve. We cannot expect, on the one hand, complete mixing in the ventricle, and on the other, complete bolus movement of cold water to the ventricle without mixing in the atrium, even though the injection port in the atrium is just above the tricuspid valve. Irrespective of injection site, newly entering atrial blood does not mix completely with the ventricular contents in anesthetized dogs.24,25 and we think that a uniform concentration in the ventricle may be hard to obtain. However, Homer and Krayenbuehl26 propose less restrictive alternative conditions for accurate measurements of diastolic volume and this is applicable also to thermal washout method. RV injection involved another problem, that is whether CO could be accurately measured. Some authors27 have reported that there is a difference in CO between RA and RV injections; however, we could not find any such difference. The cause of discrepancy between our results and theirs is not clear and more thorough investigation into this aspect is needed.

How Did Catheter Cooling Affect EF?

The effect of catheter cooling was far from our expectations (Fig 4). Clinically, the catheter will rarely be inserted as far as 90 cm on the venous side, but the EFs of the latter part of a washout curve may still be affected, as discussed earlier. Interestingly, in a study in swine, EFs obtained with jugular placement of the catheter were observed to be larger than those obtained with femoral placement, and the investigators28 considered that this phenomenon may be related.
to the distance between the thermistor and the pulmonary valve. Our results, however, clearly explain this phenomenon, namely, a longer venous distance will affect RVEF by heat transfer from the catheter wall. Heat transfer across the catheter wall is of a different nature and we think that the early part of the downslope of the washout curve obtained in RV injection is least affected by this factor.

**How Did the Injection Timing Affect RVEF?**

Stroke volumes are considered to vary stroke by stroke, but it is more reasonable to assume that they fluctuate physiologically with respiratory movement. CO could be calculated as the mean of a few strokes, and thereby might be affected less by respiration than stroke volume, as previously stated by McMillan and Morris; however, others insist that random theralmodulation measurements of CO during intermittent positive pressure ventilation should be avoided. Compared with CO, RVEF may be affected more by the respiratory cycle because the preload and afterload of the RV are largely influenced by respiratory movement. Jardin and others found that RVEF fluctuates greatly from 0.71 ± 0.19 at early expiration to 0.37 ± 0.10 at midinspiration during mechanical ventilation, determined by two-dimensional echocardiography. What is the true RVEF is the major issue, and Assmann and Falke advocate an automatically timed injection technique (sets of four determinations equally spread throughout the respiratory cycle) and a transient increase of respiratory rate. Our patients could breathe for themselves but were affected by hypoxemia, and so were treated with CPAP (see "Methods and Materials"). We did not have any data as to how this respiratory pattern would affect RVEF during the patients' respiratory cycles; however, we injected the cold water irrespective of respiratory cycle. It is unlikely that the cold water was always injected at any one point of a respiratory cycle and our data could be evaluated as representing the mean at various points through a respiratory cycle. Thermal washout method is based on the theory that successive stroke volumes are relatively constant, and thereby, it is inappropriate to investigate fluctuations in RVEF beat by beat. Further investigation with the aid of other than thermal washout methods is needed.

**What Was Clarified by Comparison of Clinical and Model Experiments?**

We did not intend to construct an analogue close to an actual heart, but a sufficient model for investigating what factors affect the thermal washout curve under the condition of complete mixing in a chamber with good heat-insulating properties and known preset EFs and our model was sufficient for these purposes. As clearly shown in Figure 3, EF1 or EF2 obtained from chamber (ventricular) injection was the closest to the actual value, inflow tract (atrial) injection apparently underestimated, and the use of EFmean also resulted in underestimation within the range investigated (EF = 0.4 to 0.62). A possible explanation for this has already been postulated above. This result could not be directly applied to the in vivo situation; however, clinical investigation with alternate RA or RV injections yielded similar phenomena. This strongly suggests that RA injection or calculation of mean value may lead to underestimation of the actual RVEF; however, we did not compare thermal RVEF with those obtained from other methods in our patients. We therefore cannot conclude which of the values from RA and RV injections is closest to the actual RVEF in this investigation. There is a good correlation of RVEF values between thermal washout method and other methods (cinevlecardiography, echocardiography, RI-angigraphy). Thermal washout method results may reflect actual RVEF, so that a good correlation with other methods is very reasonable; however, this does not mean that the method measures the true RVEF. Actually, thermal RVEF values are low compared with those obtained by other methods and since there is no gold standard for RVEF and thermal washout method can be used without assumption of RV anatomic configuration, it is important to improve the accuracy of this method.

In conclusion, when comparing the EFs obtained from RA or RV injection alternately in the same patients, RA injection was found to result in significantly low EFs. In analysis of factors affecting EFs in the model experiment, it was observed that EF1 and EF2 obtained from RV injection might be closest to the actual values because of the least interference by ventricular and catheter cooling.

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