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Mechanism for Slowing of Heart Rate and Associated Changes in Pulmonary Circulation Elicited by Cold Injectate during Thermodilution Cardiac Output Determination in Dogs

Toshiaki Nishikawa, M.D., Akiyoshi Namiki, M.D.†*

The authors investigated the mechanism for slowing of heart rate (HR) and associated changes in the pulmonary hemodynamics caused by cold injectate during thermodilution method. To clarify whether the slowing of HR after cold injectate is due to the cooling of the sinoatrial (SA) node or a reflex mediated by the autonomic nerves, we directly measured the myocardial temperature of the SA node region by a thermistor probe, and evaluated the HR responses to iced injectate after autonomic blockade in anesthetized dogs. Additionally, pulmonary blood flow (PBF) was continuously measured by an electromagnetic flowmeter during the delivery of injectate. The direction and magnitude of changes in HR after injectate were significantly dependent upon the injectate temperature ($P < 0.01$). Thereby, the changes in HR correlated well with those in myocardial temperature of the SA node region ($r = 0.987$, $P < 0.01$). However, the HR responses to injectate were unaffected by cervical vagotomy or stellate ganglionectomy. A significant decrease in PBF was noted in most cases during the slowing of HR. It was concluded that the slowing of HR after cold injectate during thermodilution in dogs is primarily due to the direct cooling of the SA node. (Key words: Complications: dysrhythmia. Heart: cardiac output; heart rate; pulmonary blood flow; thermodilution. Parasympathetic nervous system: vagotomy; vagus. Sympathetic nervous system: stellate ganglion; sympathectomy. Temperature: cooling.)

SEVERAL REPORTS HAVE stated that administration of cold injectate during thermodilution cardiac output measurement elicits hemodynamic changes in humans, *i.e.*, slowing of heart rate (HR), decreased blood pressure, and arrhythmias.[1–5] Harris *et al.*[2] observed that a decrease of 10% or greater of pre-injection HR occurred following 10 ml of iced injectate in 14 out of 63 adult cardiac surgical patients (22%). Of these hemodynamic changes, sinus slowing has been thought to be a cold-temperature-mediated response,[1,2] in spite of the fact that no definite evidence demonstrates that the cold injectate directly cools the SA node resulting in a deceleration of HR. Furthermore, it is not clear whether the slowing of HR is a reflex *via* the autonomic nerves that is initiated by cold or mechanical stimuli.

* Instructor in Anesthesiology. Presently Assistant Professor, Institute of Clinical Medicine, University of Tsukuba, Sakuramura, Ibaraki.

† Professor and Chairman of Anesthesiology.

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Address reprint requests to Dr. Nishikawa: Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Sakuramura, Ibaraki 305, Japan.

The stability of the pulmonary circulation is a major premise during cardiac output measurement by thermodilution.[6,7] In this respect, if the slowing of HR after injectate could elicit changes in the pulmonary blood flow (PBF), it follows that these circulatory perturbations may become one of the factors leading to an erroneous estimation of cardiac output measurement.

Thus, this study was undertaken to clarify the mechanism for slowing of HR after cold injectate and to investigate the effects of cold injectate upon the pulmonary circulation in anesthetized dogs.

Materials and Methods

General Procedures

Experiments were performed in 38 adult mongrel dogs of either sex, weighing from 8–12 kg. After all animals were anesthetized with intravenous pentobarbital sodium 30 $mg \cdot kg^{-1}$, the trachea was intubated and they were mechanically ventilated with room air and supplemental oxygen through a cuffed endotracheal tube, using a volume-cycled animal ventilator (R-60, Aika, Tokyo). Anesthesia was maintained with a constant infusion of thiamylal 2 $mg \cdot kg^{-1} \cdot h^{-1}$, and pancuronium 0.1 $mg \cdot kg^{-1}$ was administered as needed to produce immobilization. To reduce pain, all skin incisions were infiltrated with 5–10 ml of 1% lidocaine. During all measurements, esophageal temperature was maintained between 36.5 and 38.5° C. Sodium bicarbonate was given as needed to maintain a normal buffer base.

A catheter was advanced through the right external jugular vein so that its tip lay at the junction of the superior vena cava and right atrium. This was used for administration of lactated Ringer's solution at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ and 5% dextrose in water as injectate. Lead II of an electrocardiogram (ECG) was monitored with subcutaneous electrodes introduced in the legs. HR was measured by a cardiotachometer triggered by lead II of the ECG. Arterial blood pressure (AP) measurements and blood gas samples were obtained from a femoral arterial catheter. A flow-directed balloon-tipped pulmonary artery catheter was inserted *via* a femoral vein for continuous measurement of pulmonary artery pressure (PAP). Another catheter was positioned in the right atrium through the left external jug-

ular vein to permit continuous monitoring of the right atrial pressure (RAP). Calibrated Statham P231D transducers (Gould, USA) were used for pressure measurements.

Measurement of Myocardial Temperature of the SA Node Region

The effects of injectate temperature upon the myocardial temperature of the SA node region were determined in ten dogs. After a right-sided thoracotomy was performed in the fourth interspace and the pericardium incised, a thermistor probe with thermal time constant of 0.5–1.5 s (needle type, Terumo, Tokyo) was inserted into the SA node region (the right atrium at its junction with the superior vena cava) at a depth of approximately 0.5 mm for continuous measurement of myocardial temperature by a thermometer (CTM-201, Terumo).

Following surgical preparations, all dogs were allowed a stabilization period of at least 60 min. After this period, four injections of 10 ml, 5% dextrose in water (iced [0–2° C], room temperature [RT, 22–25° C], 37° C, and 42° C) were administered manually through the right external jugular catheter. The myocardial temperature of the SA node region, ECG, AP, HR, PAP, and RAP were continuously recorded on an eight-channel polygraph system (Nihon-Kohden, Tokyo) until all parameters returned to pre-injection levels. Maximal changes in the myocardial temperature of the SA node region and HR were obtained for each injection. Changes in HR were plotted against those in the myocardial temperature of the SA node region. A correlation coefficient and a linear regression equation were calculated. The sequence of administration for each injectate was randomized. Data were discarded and a second injection was made if an extrasystole appeared during or after an injection. The time required for delivering the 10-ml injectate was approximately 6–8 s.

Autonomic Blockade

The effects of right or bilateral cervical vagotomy upon the hemodynamic responses to 10 ml iced injectate were evaluated in the ten dogs subjected to the measurement of myocardial temperature of the SA node region. After both vagosympathetic trunks were carefully dissected free at the level of the thyroid cartilage in the neck, control measurements were made using 10 ml iced, RT, and 37° C injectate. Thereafter, the same procedure was repeated by using 10 ml iced injectate after the transection of the right and, subsequently, the left (bilateral) vagosympathetic trunk. Hemodynamic changes following 10 ml iced injectate in the intact state were compared with those after right and bilateral cervical vagotomy.

In another ten dogs, hemodynamic changes were observed after sympathectomy to assess the influence of sympathetic tone upon the slowing of HR and other hemodynamic changes caused by cold injectate. After the chest was opened by a midsternal incision, bilateral stellate ganglia were dissected free, and isolated. After hemodynamic responses to 10 ml iced, RT, and 37° C injectate were obtained, both stellate ganglia were completely excised. Loss or attenuation of sympathetic activity was confirmed by the carotid sinus reflex (bilateral occlusion of common carotid arteries for 60 s). The hemodynamic responses to 10 ml iced injectate were compared with those before sympathectomy.

Measurement of Pulmonary Blood Flow

Eighteen dogs were studied to investigate the effects of cold injectate temperature and volume (*e.g.*, 3, 5, and 10 ml iced, and 10 ml RT injectate) upon pulmonary blood flow (PBF) and other hemodynamic parameters. After the pulmonary trunk was dissected free of the surrounding tissues through left-sided thoracotomy in the fourth interspace, an electromagnetic flow probe of appropriate size (FC type 10–12 mm, Nihon-Kohden) was carefully placed around the pulmonary trunk for continuous measurement of PBF. The flow probe was calibrated *in vitro* prior to implantation, and PBF was measured continuously with a square-wave electromagnetic flowmeter (MFV-1200, Nihon-Kohden), together with other hemodynamic parameters before and after administration of injectate (3, 5, 10 ml iced, and 10 ml RT). All injections were started at end inspiration. The time for delivering the 10 ml injectate was the same as that employed in the above experiments, while that for 3 or 5 ml injectate was less than 2 and 4 s, respectively.

Analyses of Data

All values were expressed as mean ± SD. Paired Student's *t* test was used to determine statistical significance for paired data. Unpaired data were analyzed by analysis of variance and unpaired Student's *t* test. A correlation coefficient and a linear regression equation between two variables were calculated by the method of least squares. Results were considered statistically significant if P values were less than 0.05.

Results

Figure 1 shows representative polygraph tracings of hemodynamic variables and the myocardial temperature of the SA node region after 10 ml iced injectate. It is evident that this injection was associated with parallel change in HR and myocardial temperature of the SA node region, along with decreased AP and PAP, and increased RAP.

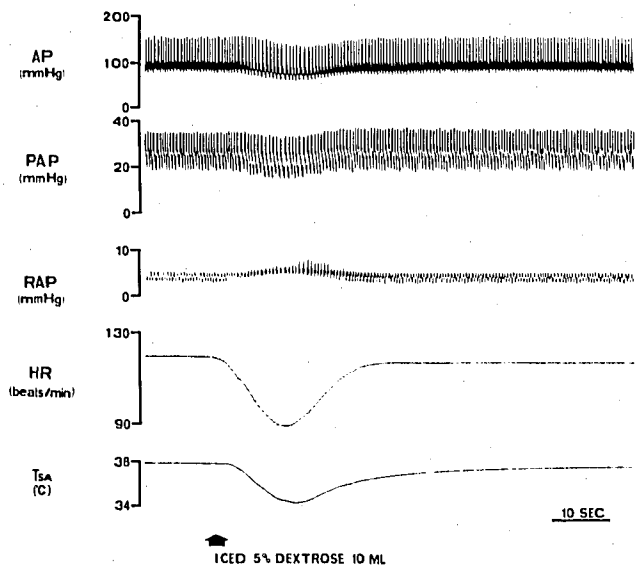

FIG. 1. Representative polygraph tracings of arterial blood pressure (AP), pulmonary artery pressure (PAP), right atrial pressure (RAP), heart rate (HR), and myocardial temperature of the sinoatrial node region (T_{SA}) after 10 ml iced injectate. Note transient simultaneous changes in HR and T_{SA}, associated with decreased AP and PAP, and increased RAP.

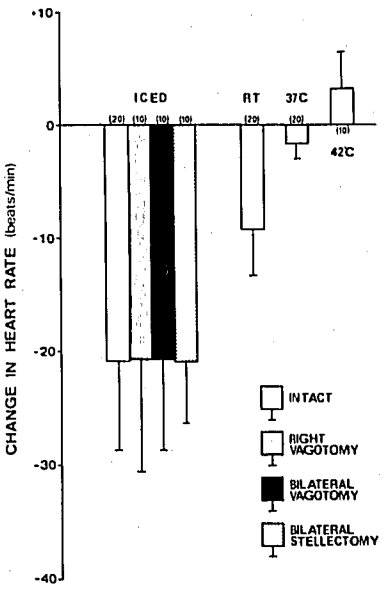

FIG. 2. Changes in heart rate after 10 ml iced, room temperature (RT), 37° C, and 42° C injectate, and heart rate responses to 10 ml iced injectate after vagotomy or stellectomy. All n in the parentheses represent the number of dogs studied. Heart rate significantly decreased following the administration of 10 ml iced, RT, and 37° C injectate ($P < 0.01$), whereas an increased heart rate was noted after 10 ml of 42° C injectate ($P < 0.05$). Thus, the direction and magnitude of changes in heart rate was dependent upon the injectate temperature. However, autonomic blockade had little influence upon the heart rate responses to 10 ml of iced injectate.

Injectate of 10 ml iced, RT, and 37° C produced significant decreases in HR by means of 21 ± 7, 9 ± 3, and 2 ± 1 beats · min^{-1}, respectively, ($P < 0.01$) as shown in figure 2. In contrast, HR significantly increased by a mean of 3 ± 3 beats · min^{-1} after 10 ml, 42° C injectate ($P < 0.05$). Accordingly, the magnitude and direction of changes in HR after injectate were dependent on the injectate temperature ($P < 0.01$). Further, the same decrement in HR with 10 ml iced injectate was also observed after right and bilateral cervical vagotomy, and bilateral stellectomy (fig. 2).

Maximal changes in HR plotted against those in myocardial temperature of the SA node region are shown in figure 3. The line of regression represents the line of best fitted through the scatter and the equation for this line was $y = 7.07x - 0.79$. The coefficient of correlation between the two variables was 0.987 ($P < 0.01$).

During slowing of HR after 10 ml iced injectate, mean arterial pressure (MAP), and mean pulmonary artery pressure (MPAP) significantly decreased as shown in table 1. Conversely, RAP significantly increased during the slowing of HR. However, these hemodynamic responses to 10 ml iced injectate were not affected by cervical vagotomy or stellectomy. Ten milliliters of RT injectate produced smaller decreases in MAP and MPAP than 10 ml iced tracer during the slowing of HR. For 10 ml 37° C and 42° C injectate, only slight increases in MAP and MPAP were found after an injection. Further, the magnitude of increases

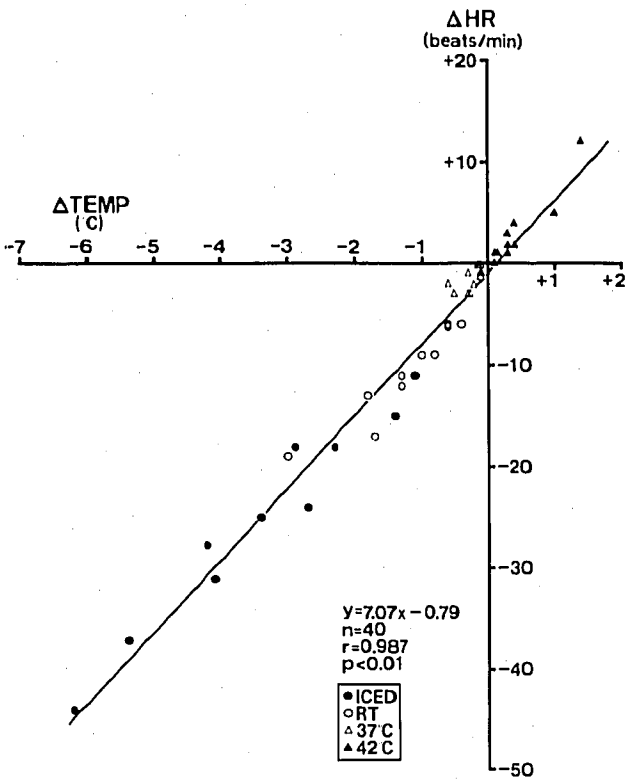

FIG. 3. Relationship between maximal changes in myocardial temperature of the sinoatrial node region (ΔTEMP) and those in heart rate (ΔHR) measured simultaneously after 10 ml iced, room temperature (RT), 37° C, and 42° C injectate. A good correlation was obtained between the two variables, with changes in myocardial temperature plotted on the abscissa, and those in heart rate plotted on the ordinate.

TABLE 1. Effects of 10 ml of Iced Injectate on Mean Arterial Pressure (MAP), Mean Pulmonary Artery Pressure (MPAP), and Right Atrial Pressure (RAP) Before and After Autonomic Blockade

		Cervical Vagotomy (n = 10)			Bilateral Stellectomy (n = 10)	
			Post			
		Pre	Right	Bilateral	Pre	Post
MAP (mmHg)	Control	126 ± 15	132 ± 14	140 ± 18	111 ± 29	84 ± 17
	Maximal Change	119 ± 16*	126 ± 15*	132 ± 18*	105 ± 26†	75 ± 18*
MPAP (mmHg)	Control	18.4 ± 3.3	19.0 ± 2.6	20.1 ± 4.5	17.0 ± 6.1	19.0 ± 4.4
	Maximal Change	17.6 ± 2.7†	18.4 ± 2.6†	19.2 ± 4.6†	16.3 ± 5.9†	17.4 ± 4.1*
RAP (mmHg)	Control	6.5 ± 1.8	6.0 ± 2.4	6.5 ± 3.5	5.5 ± 2.1	6.8 ± 2.7
	Maximal Change	6.7 ± 1.7†	6.4 ± 2.5†	6.9 ± 3.8†	5.8 ± 2.2†	7.3 ± 2.9*

Values are given as mean ± SD.
* $P < 0.01$ compared with control value.
† $P < 0.05$ compared with control value.

in RAP after injectate was comparable among the injectate at different temperatures (iced, RT, 37° C, and 42° C).

Table 2 shows the mean values of control and lowest values in PBF, MPAP, and HR for all four injectates. PBF decreased after 10 ml iced injectate in most dogs. Other injectate also produced smaller but significant reductions in PBF at the slowing of HR, with the exception that 10 ml RT injectate showed insignificant changes. The percent of control achieved in PBF during the slowing of HR after 3, 5, and 10 ml iced injectate were 96.0 ± 4.2%, 94.1 ± 6.1%, and 89.5 ± 8.7%, respectively ($P < 0.01$).

Discussion

This experiment demonstrates that the slowing of HR following cold injectate is mainly due to the direct cooling of the SA node, rather than a reflex mediated by the autonomic nerves, or the effect of pressure exerted against the SA node.

Our expectation was that the slowing of HR and the other associated hemodynamic changes after cold tracer were a result of the direct cooling of the SA node or by a reflex elicited by cold or mechanical stimuli and mediated through the activation of cholinergic discharge or inhibition of adrenergic discharge. The dependence of direction and magnitude of HR changes upon the temperature of the injectate (fig. 2), and a good correlation obtained between changes in HR and those in myocardial temperature of the SA node region (fig. 3) confirmed that the cooling of the SA node is responsible for the HR slowing after cold injectate. Previous reports suggested that the intrinsic rhythmicity of the SA node can be reduced by hypothermia.[8–10] Marshall[8] showed that lowering the temperature caused slowing of the atrial rate in association with a fall in the diastolic membrane potential and action potential in pacemaker fibers of the rabbit atrium.

In the present study, cervical vagotomy or stellectomy failed to abolish or attenuate the sinus slowing of the heart and other hemodynamic changes caused by cold injectate (table 1; fig. 2). Thus, the slowing of HR following cold injectate was proved not to be a reflex mediated by the autonomic nerves. Numerous cardio-

TABLE 2. Effects of Cold Injectate on Pulmonary Blood Flow (PBF), Mean Pulmonary Artery Pressure (MPAP), and Heart Rate (HR)

		Iced			
		3 ml	5 ml	10 ml	RT 10 ml
PBF (ml/min)	Control	935 ± 275	919 ± 275	913 ± 218	924 ± 225
	Lowest Value	904 ± 290*	874 ± 297*	829 ± 249*	916 ± 254
MPAP (mmHg)	Control	21.0 ± 4.5	20.2 ± 4.7	17.6 ± 4.7	19.2 ± 4.4
	Lowest Value	20.5 ± 4.6*	19.5 ± 4.6*	16.9 ± 4.9*	18.8 ± 4.5
HR (beats/min)	Control	143 ± 28	142 ± 28	148 ± 31	144 ± 27
	Lowest Value	137 ± 28*	132 ± 28*	127 ± 30*	136 ± 27*

Values are given as mean ± SD (n = 18).
* $P < 0.01$ compared with control value.

pulmonary reflexes originating in the heart and lungs have been investigated in earlier animal experiments,[11-15] since Bezold and Jarisch observed a cardiovascular depression following the administration of veratrum alkaloid. For instance, Aviado *et al.*[11] found that an increase in the right atrial pressure caused reflex bradycardia with peripheral vasodilation, which was abolished by cutting the vagi. On the contrary, a positive chronotropic effect by acute volume loading or direct stretch of the SA node was reported,[16-19] so that the cardiovascular response to acute distension of the right atrium has not been conclusively defined. In the present experiment, however, it is unlikely that the pressure exerted by the injectate against the SA node or the atrial wall caused the HR to slow, since the same increase in RAP was found when 10 ml injectate at different temperatures was rapidly delivered into the right atrial cavity, and there was no correlation between the changes in RAP and those in HR.

Clinically and experimentally, 3–10 ml injectate at 0° C or RT is widely used.[20-23] In order to maximize the signal-to-noise ratio in the time-temperature thermodilution curve, an injection of large amount of indicator is required.[20,21] On the contrary, the present results (table 2) suggest that larger injectate volume might reduce the confidence of calculated cardiac output values when a marked hemodynamic change does occur. However, our findings may not be applicable to humans or less important in humans, because the ratio of injectate volume to atrial size is smaller in adult human than in dogs.

In conclusion, the slowing of HR after cold injectate during thermodilution in dogs is mainly due to the direct cooling of the SA node.

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