FULL PAPER *Internal Medicine*

The Effect of 7.2% Hypertonic Saline Solution with 6% Dextran 70 on Cardiac Contractility as Observed by an Echocardiography in Normovolemic and Anesthetized Dogs

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(Received 21 May 2007/Accepted 28 September 2007)

ABSTRACT. We studied the effect of a small volume of 7.2% hypertonic saline solution (HSS) or HSS with 6% dextran 70 (HSD) on hemodynamic status, especially on cardiac contractility, in anesthetized dogs using the left ventricular end-systolic volume index (ESVI) and ejection fraction (EF), which can be obtained in noninvasive echocardiography. In the present study, the mean values of ESVI were unaffected by HSS and HSD infusion, whereas the left ventricular end-diastolic volume index (EDVI) was markedly and significant increased. As a result of the changes in EDVI but not in ESVI, EF increased transiently and significantly in the HSS and HSD group, whereas no such significant change was observed in the dogs that received isotonic saline solution. In addition, as a result of the increases in cardiac index but not arterial pressure, system vascular resistances (SVR) decreased transiently and significantly in the HSS and HSD groups, whereas no such significant change was observed in the ISS group. Therefore, the positive inotropic effects of HSS and HSD may be attributable to the increase in left ventricular preload and decreases in SVR rather than direct changes in myocardial contractility.

KEY WORDS: canine, cardiac contractility, cardiac index, echocardiography, hypertonic saline.

J. Vet. Med. Sci. 70(1): 89–94, 2008

Recent clinical data supports the concept that early restitution of the circulation in severe sepsis and septic shock patients improves oxygenation and increases the survival rate [22]. It is therefore of great importance to restore the intravascular volume and thereby maintain adequate cardiac output (CO) and oxygen delivery. Hypovolemic shock resuscitation with colloids is preferred over crystalloids because colloids result in better regional and microcirculatory blood flow [24]. Small-volume hypertonic saline solution (HSS) has been successfully used to resuscitate dogs with experimentally induced hypovolemic shock [13, 28, 29]. The beneficial hemodynamic effects of HSS have been attributed to rapid plasma volume expansion caused by body fluid shift from intracellular space [2, 7], transient decrease in systemic and pulmonary vascular resistance [27], a vagally mediated reflex dependent stimulation of pulmonary osmoreceptors [13, 30] and increased cardiac contractility [29]. These beneficial effects most likely result from an increase in preload and/or decrease in afterload [27].

Some studies have found a positive inotropic effect after HSS infusion [9, 10, 15, 17]. HSS induces cellular dehydration through an osmotic effect, thus decreasing cellular water content and directly increasing the calcium level [32]. This could produce a positive inotropic effect of HSS because the increase in intracellular calcium concentration ($[Ca^{2+}]in$) results in increased cardiac contractility. Myocardial oxygen consumption increases at the end of HSS infusion without significant change in coronary venous oxygen tension and content [15]. However, many *in vitro* studies have demonstrated that a sudden increase in the extracellular sodium concentration ($[Na^+]_{out}$) produces a transient and mild negative inotropic effect that lasts for up to 10 min, with $[Na^+]_{out}$ directly influencing cardiac contractility [3, 4, 31]. *In vivo*, HSS does not induce a demonstrable effect on M-mode echocardiograph indices of systolic function, but it does cause preload augmentation that may contribute to an abrupt and transient increase in CO just after HSS infusion in normovolemic dogs [26].

The beneficial effects of HSS are short-lived. The addition of a hyperoncotic agent, such as dextran, has been shown to prolong the cardiovascular resuscitative effect of HSS in the treatment of hemorrhagic shock [24]. Combination of 6% dexran 70 with HSS (HSD) increases the duration of action, making these solutions more efficient with regard to maintenance of plasma volume, mean arterial pressure and CO [11, 12, 19]. Adding colloids prolongs the duration of volume expansion and thereby the effects on cardiac contractility. HSD has been shown to be beneficial in experimental shock models. Further HSD research is required with regard to cardiovascular function in dogs. Therefore, there has been clinical interest in HSD in relation to its effect on cardiovascular status, especially cardiac contractility [26].

The aim of this study was to investigate using echocardiography wheter infusion of the same small volume of HSD is superior to infusion of HSS in terms of the inotropic effect in normovolemic anesthetized dogs.

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MATERIALS AND METHODS

All procedures were undertaken in accordance with the National Research Council on Guide for the Care and Use of Laboratory Animals [18]. The experiments were performed on 21 beagle breed dogs, 3.3 ± 1.6-years-old (mean ± SD), weighing 13.2 ± 3.1 kg (mean ± SD). These dogs were deemed healthy on the basis of a physical examination, thoracic auscultation and radiological and echocardiographic analyses. A complete, balanced diet consisting of rationed concentrated pellets was provided, and the dogs had unlimited access to fresh water. Food (16 hr prior) and water (1 hr prior) were removed prior to anaesthesia. All the dogs were cared for in accordance with the principles outlined in the Guidebook for the Care and Use of Laboratory Animals approved by the College of Bioresource Sciences, Nihon University.

The dogs were divided into three groups (n=7 each group). They were randomly allocated to receive 5 m*l*/kg of either isotonic saline solution (ISS), HSS or HSD at a flow rate of 20 m*l*/kg/h via right cephalic vein. Each dog was introduced by thiopental sodium (Ravonal 0.3 for injection, Tanabe Seiyaku, Osaka, Japan) at a dose of 18 mg/kg intravenously, and anaesthesia was maintained with isoflurane (Forane, Abbott Japan, Tokyo, Japan) in 100% oxygen. During the experiment period, isoflurane in oxygen was delivered at an end-tidal concentration of 1.8 ± 0.1%. The time of initiation of fluid infusion was designated as t=0. All dogs were monitored until the end of the experiment (t=90 min).

Transesophageal echocardiograph images of the long axis 2 and 4 chamber views were obtained at t=0 (pre), 3, 6, 9, 12, 15, 30, 45, 60 and 90 min after initiation of fluid infusion using an echocardiograph (Prosound SSD-4000 Plus, Aloka, Tokyo, Japan) with a 5.0 MHz transesophageal probe (UST-5293S-5, Aloka). An anaesthetic gas and electrocardiograph monitor (Colin BP-508 type S, Omron Colin, Tokyo, Japan) was used to monitor the systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP) by non-invasive oscillometry and heart rates (HR) by limb lead electrocardiogram at each recording point. Venous samples were obtained at t=0, 5, 10, 15, 30, 45, 60 and 90 min after initiation of fluid infusion to determine the haemoglobin concentration and hematocrit value using an automatic cell counter (Celltac-alfa, Nihon Kohden Co., Tokyo, Japan). The changes in the relative plasma volume (rPV) were calculated from haemoglobin concentrations and haematocrit values as follows [1, 25–27]:

$$\text{rPV}\ (\%) = \frac{\text{Hb}_{\text{pre}}}{\text{Hb}_{\text{samp}}} \times \frac{100 - \text{Hct}_{\text{samp}}}{100 - \text{Hct}_{\text{pre}}} \times 100,$$

where Hb_{pre} and Ht_{pre} were Hb and Ht before saline infusion and Hb_{samp} and Ht_{samp} were Hb and Ht at each sampling point.

The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were determined by the Simpson method. The stroke volume (SV), CO and ejection fraction (EF) were calculated as follows [16]:

$$\text{SV}\ (\text{m}l) = \text{EDV} - \text{ESV},$$
$$\text{CO}\ (l/\text{min}) = \text{SV} \times \text{HR},$$
$$\text{EF}\ (\%) = \frac{\text{SV}}{\text{EDV}} \times 100.$$

Then, SV, CO, EDV and ESV were indexed (SVI, CI, EDVI and ESVI, respectively) to body surface area (BSA) as follows [21]:

$$\text{BSA}\ (\text{m}^2) = (\text{body weight}^{2/3} \times 10.1)/100.$$

The systemic vascular resistances (SVR) were calculated from CO and MAP as follows:

$$\text{SVR}\ (\text{dynes}\cdot\text{s}/\text{cm}^5) = (\text{MAP} \times 80)/\text{CO}.$$

The data are expressed as means ± standard deviation. All data recorded during this study were continuous measures with normal distributions. Statistical evaluation of data included a two-way repeated measures analysis of variance (ANOVA), with treatment group and time as the two factors, followed by use of a post hoc test that depended on multiple comparisons versus pre-value (Bonferroni test). We used ANOVA for repeated measures followed by Tukey's Studentized range test to assess differences among the three groups at each same point. These statistical analyses were performed using a software package (Stat View, Japanese Edition, Ver. 5, Hulinks Japan, Tokyo, Japan). $P<0.05$ was taken as the level of significance.

RESULTS

Figure 1 shows sequential changes in rPV, EDVI, ESVI and SVR for the dogs in each group. There was a slight increase in the rPV of the ISS group, reaching 110.5 ± 5.0% at t=15 min when the fluid infusion was completed, and this value remained stable for the rest of the experiment. For the HSS and HSD groups, progressive and significant increases in the rPV were observed that reached peaks of 137.3 ± 6.4% at t=15 min and 141.2 ± 7.8% at t=30 min after initiation of the fluid infusion ($p<0.001$). The sequential change in rPV in the HSD group was significantly greater than those of the other groups ($p<0.001$).

EDVI increased immediately after HSD infusion from 43.2 ± 8.7 at prior to infusion to 53.4 ± 10.2 mL/m^2 at 15 min after initiation of fluid infusion ($p<0.001$). Compared with the ISS and HSS groups, the HSD group had significantly higher volumes persisted for the rest of the experiment ($p<0.001$). The mean values of ESVI were unaffected by ISS, HSS or HSD infusion and remained constant throughout the experiment in all groups.

The SVR of the ISS group was unaffected by ISS infusion and remained constant throughout the experiment. The SVRs of the HSS and HSD groups, however, were progressively and significantly decreased, from pre-values of

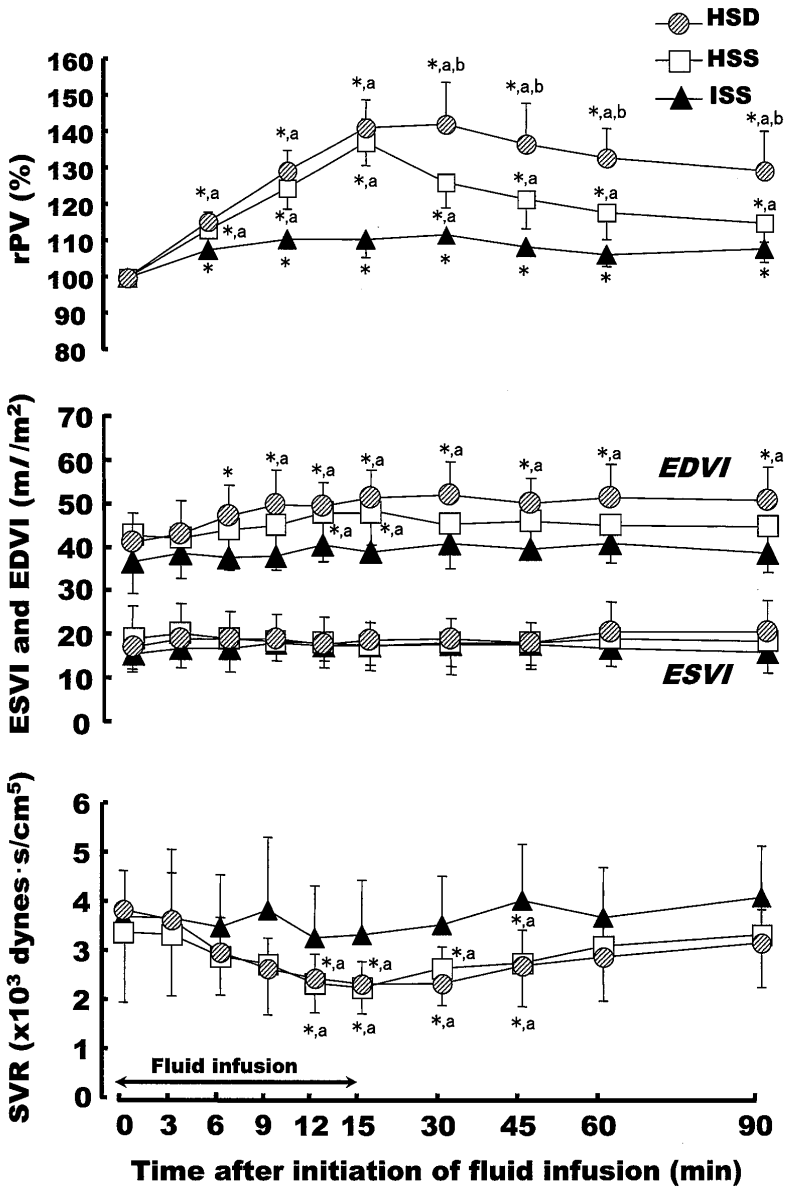

Fig. 1. Sequential changes in a relative plasma volume (rPV), left ventricular end-systolic volume index (ESVI), left ventricular end-diastolic volume index (EDVI) and systemic vascular resistance (SVR) after infusion of hypertonic saline dextran solution (HSD) into dogs. The levels of significance ($p<0.05$) are indicated as follows: (a) versus the ISS group, (b) versus the HSS group and (*) versus the pre-value by Bonferroni test. The data are means ± SD of seven dogs per group.

3390.6 ± 1429.9 and 3847.5 ± 797.7 dynes·s/cm^5, reaching 2261.8 ± 532.7 and 2335.6 ± 429.0 dynes·s/cm^5 at t=15 min, respectively ($p<0.01$). The SVRs of the HSD and HSS groups were significantly lower than the ISS group from 9 min to 45 min after initiation of fluid infusion ($p<0.01$). The sequential changes in arterial pressure are shown in Table 1; arterial pressure did not vary significantly during the experiment between the dogs in each group.

Figure 2 shows the sequential changes in SVI, CI and EF in the dogs of each group. The pre-values of SVI and CI of all dogs were 23.0 ± 5.5 m*l*/m^2 and 2.61 ± 0.64 *l*/min/m^2, respectively. The mean values of SVI and CI were unaffected by ISS infusion and remained constant throughout the experiment. Prior to infusion and at t=12–30 min after initiation of the HSS infusion, the mean SVI and CI significantly increased from 23.7 ± 8.3 to 30.3 ± 4.1 m*l*/m^2 ($p<0.05$) and from 2.90 ± 0.66 to 3.89 ± 0.42 *l*/min/m^2 ($p<0.05$), respectively. Then, SVI and CI decreased towards the pre-values during the experimental period. There were progressive and significant increases in the SVI and CI of the HSD group, reaching 32.2 ± 5.6 m*l*/m^2 and 3.98 ± 0.78 *l*/min/m^2, respectively, at t=30 min after initiation of HSD infusion, and these values remained unchanged for the rest of the experiment ($p<0.001$). Compared with the ISS and HSS groups,

Table 1. Effect of a small-volume of 7.2% hypertonic saline with 6%dextran 70 on cardiovascular parameters

	Pre	3	6	9	12	15	30	45	60	90 (min)
Heart rates (bpm)										
ISS	105.8±11.7	101.8±17.2	106.2±11.3	103.8±12.5	103.8±13.2	102.5±13.9	106.3±11.9	106.3±16.2	104.8±15.2	104.5±13.8
HSS	127.0±17.9	126.5±17.5	128.5±19.3	129.1±20.8	130.5±21.6	131.0±23.4	127.4±24.8	125.0±22.6	123.6±20.2	119.6±20.6
HSD	112.1±16.8	110.0± 16.3	114.3±12.4	120.1±22.9	122.9±30.8	124.0±30.0	124.1±27.1	121.7±25.1	116.6±19.1	114.4±17.2
Systolic arterial pressure (mmHg)										
ISS	110.0±7.8	108.3±5.4	113.3±15.5	117.5±25.3	119.8±27.6	119.2±31.2	123.7±21.0	125.2±8.3	127.2±6.5	126.7±8.1
HSS	111.7±33.9	108.6±25.0	108.3±28.5	106.3±29.5	106.7±28.4	107.6±25.7	106.7±17.6	108.7±17.1	111.4±22.8	115.3±24.9
HSD	110.1± 29.0	107.4±23.7	105.4±20.2	105.1±20.3	105.7±21.8	102.4 ±17.1	106.1±19.4	111.1± 21.4	110.4±19.4	115.0±22.0
Mean arterial pressure (mmHg)										
ISS	64.8±14.1	64.0±11.4	60.0±8.7	58.8±13.6	57.4±12.4	58.3 ±13.4	64.8±14.1	76.4±16.9	76.6±14.7	78.4±15.7
HSS	62.2±15.1	62.2±13.7	61.5±14.8	61.0±15.0	60.3±14.4	63.3±10.2	64.5±12.6	66.5±13.0	69.7±16.3	72.5±19.4
MSD	66.3± 9.5	62.7±8.5	61.3±7.0	60.8±7.4	60.5±9.0	60.8±6.9	62.2±8.2	68.0±6.7	70.5±5.7	71.7±13.0
Diastolic arterial pressure (mmHg)										
ISS	51.4±7.0	51.6±8.6	57.2±15.9	48.8±9.9	48.0 ±8.6	48.3±9.8	50.5±11.2	59.4±12.1	58.8±10.9	59.6±10.2
HSS	51.2±8.9	50.8±9.8	49.5±10.5	49.0±9.6	48.8±9.8	50.0±8.9	52.2±8.8	53.0±9.1	54.8±12.0	56.7±13.5
HSD	56.8±4.9	541±11.7	52.9±8.4	51.1±6.2	50.7±7.0	51.1±8.1	50.4±6.7	51.3±5.7	54.9±7.7	56.9±8.6

the HSD group had significantly higher volumes for SV and CI persisted for the rest of the experiment ($p<0.001$). The mean values of heart rate (HR) in the HSS and HSD groups were slightly, but not significantly accelerated (Table 1).

In the ISS group, EF did not vary significantly during the experiment. A transient and significant increase in EF was observed after hypertonic solution infusion, from 56.1 ± 9.1% to 64.0 ± 4.4% in the HSS group and from 58.2 ± 8.6% to 63.9 ± 6.3% in the HSD group ($p<0.05$). Then, EF returned to the pre-values levels by t=60 min after initiation of the infusion in both groups. No significant difference in EF was observed between the HSS and HSD groups.

DISCUSSION

Whether or not hypertonic saline with or without dextran enhances cardiac contractility is a controversial issue in research concerning shock resuscitation. Sirieix *et al.* [23] demonstrated that in patients who have undergone mitral valve repair, postoperative infusion of HSS increases left ventricular preload, decreases systemic vascular resistances and improves left ventricular EF. Some researchers have reported positive effects of HSS on cardiac contractility [9, 10, 15, 17], whereas others have not observed such positive inotropic effects [6, 20]. In the present study, the mean values of ESVI were unaffected by HSS and HSD infusion, whereas the mean values of EDVI were markedly and significantly increased. As a result of changes in EDVI but not in ESVI, EF increased transiently and significantly in the HSS and HSD groups, whereas no such significant change was observed in the ISS group. In addition, as a result of increases in CI but not in arterial pressure, SVR decreased transiently and significantly in the HSS and HSD groups, whereas no such significant change was observed in the ISS group. Therefore, the positive inotropic effects of HSS and HSD may be attributable to the increase in left ventricular preload and decrease in SVR rather than direct changes in myocardial contractility. In addition, these results suggested that 5 m*l*/kg of HSD is superior to an isovolume of HSS in terms of intropic effects in the dog.

Our results indicated that HSS and HSD infusions induced a transient, but significant increase in SVI during fluid infusion. This may be explained in part by the findings that HSS administered IV did not show any ESV alternations, whereas there was a significant increase in EDV due to preload augmentation. These results are in agreement with previous studies, which showed that resuscitation of shocked animals with HSS caused a significant increase in SV [5, 10, 28]. Those results suggest that the increases in rPV and EDVI, as indices of preload caused by HSS and HSD infusion, induced the increases in SVI to manage the volume-load, resulting in the increase in CI.

The percent fractional shortening, which can be obtained from M-mode echocardiography, is dependent on the inherent preload and afterload [16]. Horton and Mitchell [8] examined left ventricular dimensional changes during hemorrhagic shock and found that the changes in left ventricular geometry were related to a disproportionate decrease in the septal-lateral axis that was greater than that in the apex-base axis. Therefore, echo-derived ESVI and EF obtained by the Simpson method are useful parameters for estimation of LV functions without the influence of preload augmentation. In this study, the ESVI was also unaffected by HSS or HSD infusion and remained constant throughout the experiment despite satisfactory plasma volume and EDV expansion. These results are in agreement with previous studies showing that HSS does not enhance cardiac contractility [6, 20]. This may be explained in part by findings that HSS or HSD administered IV is diluted within a short period and equilibrated within the systemic circulation [14], and so its contractile effect may not be persistent enough to be detected [20].

The changes in the hemodynamic parameters, such as rPV, EDVI and CI, just after HSS and HSD infusion showed

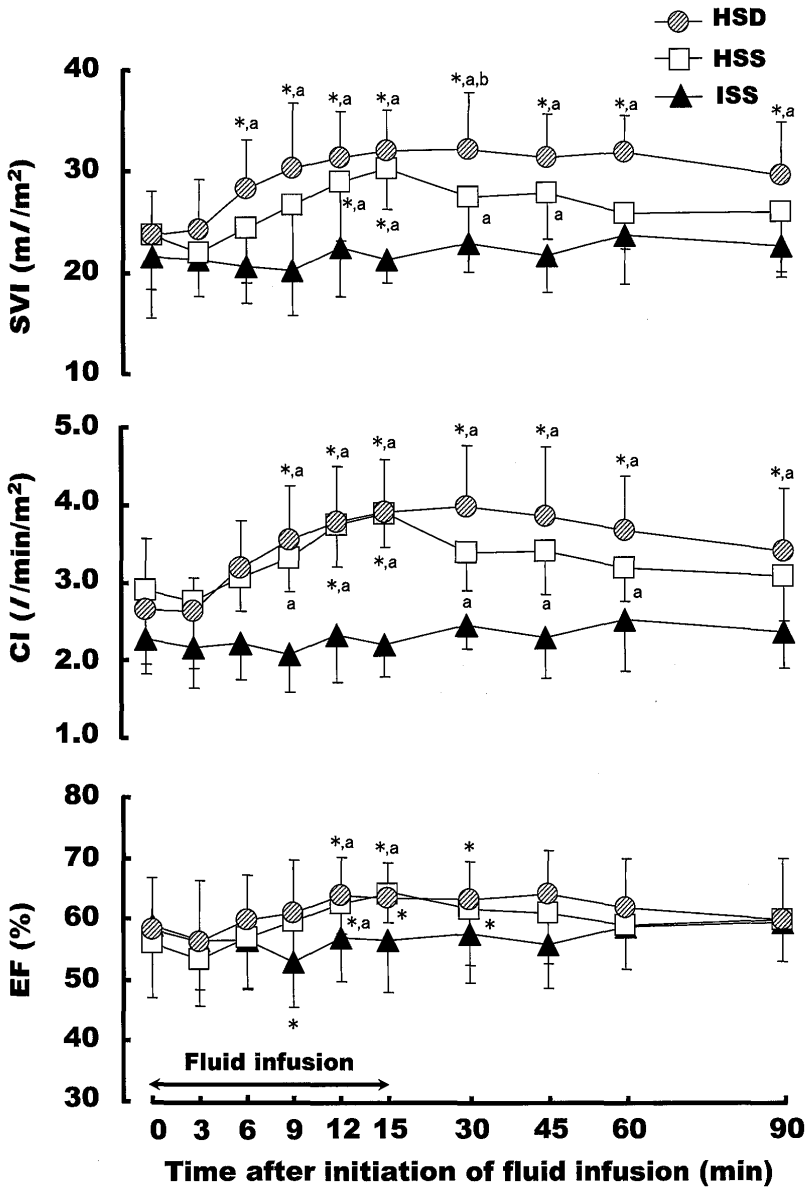

Fig. 2. Sequential changes in stroke volume index (SVI), cardiac index (CI) and ejection fraction (EF) after infusion of hypertonic saline dextran solution (HSD) into dogs. The levels of significance ($p<0.05$) are indicated as follows: (a) versus the ISS group, (b) versus the HSS group and (*) versus the pre-value by Bonferroni test. The data are means ± SD of seven dogs per group.

that there was a tendency for them to increase compared with the ISS group. The increase in CI of the dogs receiving hypertonic saline may have been due to an increase in preload [9]. In fact, many researchers have reported a significantly expanded plasma volume as a result of HSS infusion [1, 29]. In our study, HSS infusion induced a progressive and significant increase in rPV and EDVI at t=15 min, which was the infusion ended. Because CI was calculated using HR and SVI, this implies that SVI was the factor involved in the increased CI. It is known that isoflurane anaesthesia has an influence on cardiac function. However, no changes were observed in the SVRs of the dogs in the ISS group, which were administered isotonic sodium chloride solution, while they were under isoflurane anaesthesia during the experimental period. Therefore, it did not seem necessary to consider the influence of isoflurane anaesthesia on cardiac function in the present study.

The present study demonstrated that the mean values of ESVI were unaffected by HSS and HSD infusions, whereas the mean values of EDVI were markedly and significantly increased after HSS and HSD infusions. Therefore, the positive inotropic effects of HSS and HSD may have been attributed to an increase in left ventricular preload and a decrease in SVR, without direct changes in myocardial contractility.

ACKNOWLEDGMENT. This work was partially supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan Grants-in-Aid for Scientific Research (No. 15780204 and 18580319) and the Nihon University Research Grant (2006) to K. Suzuki.

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