Oxygen Delivery and Consumption during Hypothermia and Rewarming in the Dog

Jeffrey P. Morray, M.D.,* Edward G. Pavlin, M.D.†

Changes in oxygen consumption ($\dot{V}_{O_2}$) and oxygen delivery (D_{O_2}) were compared in three groups of paralyzed, sedated dogs: 1) a group (n = 5) cooled to 29° C and immediately rewarmed to 37° C; 2) a group (n = 5) cooled to and maintained at 29° C for 24 h, and then rewarmed; and 3) a group (n = 5) maintained at 37° C for 24 h. During the cooling phase, in both the acute and prolonged hypothermia animals, $\dot{V}_{O_2}$ and D_{O_2} decreased significantly from control values ($P < 0.05$). The decrease in D_{O_2} occurred as a result of a similar decrease in cardiac index (CI; $P < 0.05$) that was associated with a significant increase in systemic vascular resistance index (SVRI; $P < 0.05$). Arteriovenous oxygen content difference ($C(a-v)_{O_2}$), O_2 extraction ratio, mixed venous oxygen tension ($P\bar{v}_{O_2}$), pH, and base deficit (BD) were not different from control values even during prolonged hypothermia. Normothermic control dogs also demonstrated a significant decrease in CI ($P < 0.05$) at 24 h. Surface rewarming increased $\dot{V}_{O_2}$ back to control values in the acute hypothermia group and to values above control ($P < 0.05$) in the prolonged hypothermia group. D_{O_2} remained below control in both groups, resulting in a significant increase in O_2 extraction ($P < 0.05$) and a decrease in $P\bar{v}_{O_2}$ ($P < 0.05$) in the prolonged hypothermia animals. Following rewarming administration of sodium nitroprusside returned D_{O_2}, CI, and SVRI to control values but did not increase $\dot{V}_{O_2}$. All animals survived the study without need for inotropic support. The heart and peripheral vasculature appear to be responsive to direct vasodilation when, with rewarming, residual excess afterload prevents oxygen delivery from matching oxygen requirement. (Key words: Anesthetic techniques: induced hypotension; nitroprusside. Heart: cardiac output. Oxygen: consumption; delivery. Temperature: hypothermia.)

HYPOTHERMIA, secondary to environmental exposure,[1] or to iatrogenic attempts to protect the brain[2,3] or heart[4] from periods of hypoxia or ischemia is associated with a decrease in oxygen consumption $\dot{V}_{O_2}$ and a proportional decrease in cardiac index (CI). Thus, a 10° C decrease in core temperature reduces both $\dot{V}_{O_2}$ and CI by approximately 50%[5] and arteriovenous oxygen content difference ($C(a-v)_{O_2}$) remains constant. However, Steen et al.[6] found that in dogs cooled to 29° C for 24 h, the decrease in CI exceeded the decrease in $\dot{V}_{O_2}$, causing a mismatch between the demand for and the supply of oxygen. During rewarming $\dot{V}_{O_2}$ increased although not back to control

values), whereas CI did not respond, thereby increasing the discrepancy between the two and resulting in severe tissue hypoxia and acidosis; death occurred in some of the animals. A similar phenomenon has been reported during rewarming following prolonged hypothermia in humans.[7] By contrast, rewarming following acute hypothermia, as during cardiopulmonary bypass, is generally well tolerated.[8]

How can this apparent difference in the response to acute *versus* prolonged hypothermia be explained, and why does it persist into the rewarming period? Prolonged hypothermia may result in exceedingly high systemic vascular resistance index (SVRI),[6] which may limit cardiac output and therefore oxygen delivery (D_{O_2}) during rewarming. Another possibility is that the myocardium is directly depressed during hypothermia and cannot increase its output to meet the increased demands during rewarming. Finally, the observation in the Steen et al.[6] dogs that $\dot{V}_{O_2}$ failed to return to control values during rewarming raises the possibility that $\dot{V}_{O_2}$ was being limited by oxygen supply. Cain and Bradley[9] and Schumaker et al.[10] have demonstrated abnormalities of oxygen extraction during hypothermia in rats and dogs, respectively. Thus, it is possible that shock-like states during rewarming result not only from an inadequate CI but also from an inability to increase oxygen extraction to compensate for poor output.

The purposes of our study, therefore, were as follows: 1) to assess the differences in D_{O_2} and $\dot{V}_{O_2}$ between acute *versus* prolonged hypothermia and rewarming in dogs; 2) to assess the reversibility of the hypothermia-associated changes in CI and SVRI by administering the direct-acting vasodilator sodium nitropusside following rewarming (Specifically, we wanted to determine if the peripheral vasculature was capable of responding to a direct vasodilator, and if so, if the heart was capable of increasing its output in the face of decreased afterload; and 3) to assess whether or not increasing D_{O_2} would result in an increase in $\dot{V}_{O_2}$.

Materials and Methods

Fifteen unmedicated, fasted mongrel dogs weighing 15–22 kg were anesthetized with 3% halothane, 50% nitrous oxide, and oxygen. The trachea was intubated with a 7.0 cuffed endotracheal tube without the use of muscle relaxants. The inspired halothane concentration was de-

creased to 2% and the nitrous oxide was discontinued. Mechanical ventilation was initiated with a Harvard® pump using tidal volumes of 13–15 ml/kg and a respiratory rate sufficient to maintain end-tidal carbon dioxide concentration at 35–45 mmHg. The electrocardiogram was measured continuously. A temperature probe was inserted in the distal esophagus for continuous measurement of core temperature. An arterial cannula was inserted via cutdown in the foreleg and threaded into the thoracic aorta. A 7-Fr balloon-tipped thermodilution catheter was passed via cutdown in the external jugular vein into the pulmonary artery. A urinary bladder catheter was inserted. All animals received a continuous infusion of 5% dextrose in 0.45% saline at 2.5 ml·kg⁻¹·h⁻¹. Following monitor placement halothane was discontinued and infusions of pancuronium 0.1 mg·kg⁻¹·h⁻¹ and diazepam 0.1 mg·kg⁻¹·h⁻¹ were begun and continued throughout the study period. The initial data collection, performed at least 30 min and less than 1 h after halothane was discontinued, included core temperature (T), heart rate (HR), and systemic and pulmonary arterial pressures (systolic, diastolic, and mean [MAP, MPAP]), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), thermodilution cardiac output (CO) (5 ml iced saline injectate × 3), hematocrit (Hct), and arterial and mixed venous blood gases (at 37° C). Cardiac index (CI) was calculated by dividing CO by body weight in kilograms. Hemoglobin saturation was calculated from Pa_{O_2} following correction for temperature, pH, and base deficit (BD).[11] O₂ content (CO₂) was calculated from the formula: $CO_2 = [1.39$ ml O₂/g Hb × Hb (hemoglobin) × % saturation] + [0.003 × P_{O_2}]. Oxygen consumption ($\dot{V}_{O_2}$) was calculated as the product of CI and the arteriovenous O₂ content difference (C(a-v)$_{O_2}$). Oxygen delivery (D$_{O_2}$) was calculated by multiplying CI by Ca$_{O_2}$. O₂ extraction ratio was calculated by dividing C(a-v)$_{O_2}$ by Ca$_{O_2}$. Pulmonary and systemic vascular resistance indices were calculated from standard equations.

Arterial blood samples for measurement of epinephrine and norepinephrine concentrations were placed in sodium bisulfite-containing tubes, centrifuged, and frozen until assayed. Epinephrine and norepinephrine were extracted from plasma by absorption to alumina after adding the

internal standard dihydroxybenzylamine (DHBA). Following washing to remove plasma proteins and other contaminants, the catecholamines and DHBA were eluted (75% yield) and concentrations determined by high-performance liquid chromatography using a C-18 column and electrochemical detector as previously described (LCEC Application Note No. 14, Bioanalytical Systems, West Lafayette, Indiana). The assay has a coefficient of variation of 6–10% using the internal standard to correct for any losses incurred during the extraction; the limit of detection of norepinephrine and epinephrine is approximately 100 pg/ml.

One millimeter of Evans blue dye was injected and arterial blood samples were drawn at 15, 20, and 25 min. Samples were centrifuged and the plasma spectrophotometric absorbance at 605 nm was measured. Plasma volume (PV) was estimated using Evans blue dilution as described by Gibson and Evans.[12]

Three groups, each of five dogs, were studied:

1) Acute hypothermia animals (n = 5) were surface-cooled with ice packs to T 29° C over 4 h, then surface rewarmed over 4 h with heating blankets and a radiant warming lamp to T 37° C.

2) Prolonged hypothermia animals (n = 5) were surface cooled over 4 h with ice bags to T 29° C, maintained at T 29° C for 20 h, then surface rewarmed over 4 h to T 37° C.

3) Normothermic control animals (n = 5) were maintained at T 37° C for 24 h. At the conclusion of the study period, three animals in each group were given sodium nitroprusside (NTP) 2–3 µg·kg⁻¹min⁻¹ intravenously for 30 min. Acute hypothermia animals had data collections repeated at T 29° C, 37° C, and following NTP administration; prolonged hypothermia animals at T 29° C, every 4 h while at 29° C, at 37° C, and following NTP administration; and normothermic control animals every 4 h and following NTP administration (table 1).

Differences between groups at any given study period were analyzed with a one-way analysis of variance (ANOVA) and the Student-Newman-Keuls procedure. Within each group, differences in each variable from 37° C control were analyzed with a repeated measures ANOVA

TABLE 1. Study Conditions

Group	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Period 9
Acute hypothermia (n = 5)	37° C	29° C	—	—	—	—	—	37° C	37° C NTP
Prolonged hypothermia (n = 5)	37° C	29° C 0 h	29° C 4 h	29° C 8 h	29° C 12 h	29° C 16 h	29° C 20 h	37° C 24 h	37° C NTP
Normothermic controls (n = 5)	37° C	—	37° C 4 h	37° C 8 h	37° C 12 h	37° C 16 h	37° C 20 h	37° C 24 h	37° C NTP

TABLE 2. Response to Hypothermia and Rewarming

	Group	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Period 9
Temperature (° C)	AH	36.3 ± 0.8	29.0 ± 0.3*†	—	28.9 ± 0.2*†	—	29.0 ± 0.3*†	29.3 ± 0.5*	37.3 ± 0.4	37.3 ± 0.2
	PH	37.9 ± 0.5	29.0 ± 0.3*†	28.8 ± 0.2*†	—	28.7 ± 0.2*†	—	—	37.0 ± 0.1	37.4 ± 0.2
	NC	38.2 ± 0.5	—	38.4 ± 0.4	38.4 ± 0.5	38.6 ± 0.5	38.6 ± 0.3	—	38.2 ± 0.4	37.8 ± 0.3
HR (beats/min)	AH	132 ± 49	106 ± 19	—	77 ± 16*†	—	82 ± 13*†	75 ± 19*	97 ± 18	112 ± 17§
	PH	136 ± 52	119 ± 9*†	88 ± 26*†	—	85 ± 13*†	—	—	117 ± 37	152 ± 28§
	NC	142 ± 7	—	135 ± 19	120 ± 24	141 ± 9	136 ± 13	—	124 ± 10	153 ± 26§
MAP (mmHg)	AH	112 ± 31	141 ± 25	146 ± 6*	147 ± 18*	147 ± 19*†	145 ± 18*†	152 ± 23*	125 ± 26	103 ± 5†§
	PH	106 ± 19	130 ± 10	127 ± 25	125 ± 21	115 ± 22	120 ± 19	—	127 ± 19	113 ± 8†§
	NC	125 ± 22	—	—	—	—	—	—	121 ± 18	92 ± 7*§
MPAP (mmHg)	AH	13 ± 3	14 ± 1	18 ± 2	16 ± 3	16 ± 4	15 ± 6	13 ± 5	14 ± 3	13 ± 4
	PH	20 ± 6	17 ± 6	16 ± 7	18 ± 7	21 ± 7	18 ± 6	—	18 ± 4	14 ± 2
	NC	17 ± 10	—	—	—	—	—	—	20 ± 10	21 ± 5
CI ($ml \cdot min^{-1} \cdot kg^{-1}$)	AH	385 ± 120	227 ± 86*	142 ± 64*†	107 ± 43*†	107 ± 52*†	117 ± 58*†	101 ± 55*†	173 ± 53*	331 ± 129
	PH	363 ± 56	218 ± 77*	215 ± 47*	201 ± 70*	189 ± 50*	180 ± 58*	187 ± 55*	170 ± 66*	296 ± 48§
	NC	328 ± 162	—	—	—	—	—	—	199 ± 53*	291 ± 101§
SVRI ($dyne \cdot s^{-1} \cdot cm^{-5}$)	AH	1,338 ± 378	2,837 ± 800*	5,032 ± 1,632*†	6,569 ± 1,974*†	6,935 ± 2,134*†	6,393 ± 1,814*†	7,380 ± 2,241*†	3,214 ± 1,019*	1,485 ± 341§
	PH	1,274 ± 223	2,893 ± 1,030*	2,921 ± 1,184	3,343 ± 1,480	3,404 ± 1,423	3,895 ± 2,239	3,451 ± 1,946	3,702 ± 1,783*	1,537 ± 435§
	NC	2,297 ± 1,183	—	—	—	—	—	—	3,143 ± 1,584	1,727 ± 1,034§
V_{O_2} ($ml \cdot min^{-1} \cdot kg^{-1}$)	AH	8.7 ± 4.1	3.1 ± 1.8*	2.0 ± 0.9*†	1.6 ± 0.9*†	1.3 ± 1.1*†	1.6 ± 1.2*†	1.4 ± 1.0*†	5.1 ± 2.2	7.3 ± 1.9
	PH	5.9 ± 1.8	2.5 ± 1.2*	5.0 ± 2.0	8.2 ± 5.1	7.4 ± 2.1	6.1 ± 0.9	7.0 ± 1.4	9.3 ± 1.7*†	8.6 ± 1.4*†
	NC	5.3 ± 1.1	—	—	—	—	—	—	5.0 ± 1.1	4.2 ± 2.4
D_{O_2} ($ml \cdot kg^{-1} \cdot min^{-1}$)	AH	75.7 ± 30.8	52.5 ± 16.0*	35.3 ± 11.5*	27.2 ± 12.6*	26.2 ± 13.6*	29.4 ± 14.9*	26.3 ± 14.6*	34.5 ± 9.0*	60.0 ± 17.0§
	PH	86.3 ± 23.0	57.4 ± 21.3*	52.3 ± 9.1*	48.8 ± 11.6*	42.8 ± 10.5*	42.8 ± 11.8*	40.9 ± 7.6*	40.1 ± 6.8*	79.3 ± 12.5§
	NC	75.6 ± 45.5	—	—	—	—	—	—	41.7 ± 10.7*	62.1 ± 16.1
$C(a-v)_{O_2}$ (ml/dl)	AH	3.1 ± 1.4	1.4 ± 0.9	1.6 ± 0.7	1.4 ± 0.3	1.1 ± 0.7	1.6 ± 0.6	1.8 ± 0.4	3.3 ± 2.0	2.6 ± 1.3
	PH	1.6 ± 0.4	1.2 ± 0.3	2.8 ± 1.4	4.1 ± 1.5*	4.5 ± 1.5*	3.9 ± 1.6*	4.3 ± 1.9*	6.5 ± 1.2*	3.6 ± 0.9*§
	NC	1.9 ± 1.1	—	—	—	—	—	—	3.0 ± 0.6*	1.6 ± 0.2§
O_2 extraction ratio	AH	0.17 ± 0.11	0.06 ± 0.17*	0.07 ± 0.03	0.06 ± 0.01	0.06 ± 0.03	0.06 ± 0.02	0.07 ± 0.02	0.17 ± 0.10	0.14 ± 0.08§
	PH	0.05 ± 0.03	0.04 ± 0.02	0.11 ± 0.05	0.17 ± 0.07*	0.19 ± 0.06*	0.16 ± 0.06*	0.18 ± 0.06*	0.27 ± 0.10*	0.13 ± 0.02*§
	NC	0.09 ± 0.06	—	—	—	—	—	—	0.15 ± 0.03*	0.09 ± 0.02
CVP (mmHg)	AH	1.0 ± 1.0	0.4 ± 2.3	-1.3 ± 1.1	-1.5 ± 0.7	-1.3 ± 1.5	0.7 ± 3.8	-0.6 ± 1.1	0.7 ± 2.0	-2.0 ± 0.0
	PH	0.8 ± 0.9	-1.3 ± 1.1	6.0 ± 2.2	1.0 ± 1.6	0.8 ± 1.7	0.2 ± 1.6	—	1.6 ± 2.7	1.5 ± 2.5
	NC	0.8 ± 3.2	—	—	—	—	—	—	1.8 ± 1.5	1.7 ± 2.9
PCWP (mmHg)	AH	3.0 ± 2.5	0 ± 1.4	0.4 ± 1.9	-0.8 ± 1.3	0.2 ± 1.6	0.6 ± 3.3	1.6 ± 2.1	3.5 ± 1.9	-1.3 ± 2.3
	PH	2.0 ± 1.2	0.8 ± 1.3	-0.2 ± 1.8	0.6 ± 2.1	-0.2 ± 1.9	-1.8 ± 1.8	—	0.8 ± 1.1	0.8 ± 2.2
	NC	-1.2 ± 2.4	—	—	—	—	—	—	—	—
$P\bar{v}_{O_2}$ (mmHg)	AH	71 ± 27	84 ± 25	78.6 ± 18.1	71 ± 16	68 ± 11	73 ± 14	65 ± 14	53 ± 13*	74 ± 16
	PH	96 ± 32	89 ± 34	71.0 ± 15.3	56 ± 7	55 ± 6	58 ± 9	55 ± 7	45 ± 10*	69 ± 5§
	NC	99 ± 53	—	—	—	—	—	—	60 ± 6	78 ± 1
PV (ml/kg)	AH	67 ± 9	60 ± 15	—	—	—	—	43 ± 15*	65 ± 13	127 ± 67
	PH	61 ± 16	52 ± 12	—	—	49 ± 16	—	—	51 ± 19	94 ± 11*§
	NC	57 ± 7	—	—	—	—	—	—	52 ± 11	91 ± 16*§
Epinephrine (pg/ml)	AH	1,315 ± 1,817	957 ± 1,189	807 ± 354	253 ± 279	518 ± 347	709 ± 396	409 ± 287	365 ± 53	570 ± 175
	PH	690 ± 337	787 ± 598	—	533 ± 301	—	—	—	367 ± 224	1,048 ± 1,409
	NC	1,536 ± 1,710	—	—	—	—	—	—	422 ± 278	—
Norepinephrine (pg/ml)	AH	325 ± 289	3,119 ± 4,877	—	1,635 ± 1,903	—	—	603 ± 958	534 ± 600	—
	PH	1,030 ± 868	1,590 ± 1,409	—	311 ± 313	294 ± 266	559 ± 350	265 ± 160	741 ± 811	—
	NC	306 ± 165	—	—	—	—	—	—	314 ± 112	—

following log transformation. Differences between values obtained following rewarming (period 8) and those obtained after NTP administration (period 9) were analyzed with a two-tailed Student's t test for paired data. Statistical significance was assumed for values of $P < 0.05$.

Results

Data for all three groups of animals are summarized in table 2. For both the acute and the prolonged hypothermia groups, D_{O_2}, $\dot{V}_{O_2}$, $C(a\text{-}v)_{O_2}$ and O_2 extraction ratio data are also presented as per cent of control (fig. 1).

During the cooling phase of the study, $\dot{V}_{O_2}$ decreased more quickly than did D_{O_2}; upon reaching 29° C, $\dot{V}_{O_2}$ was 36% and 42% of control for the acute hypothermia and prolonged hypothermia animals, respectively ($P < 0.05$), and D_{O_2} was 69% and 67% of control values, respectively ($P < 0.05$). Decrease in D_{O_2} occurred because of a significant decrease in CI of a similar magnitude; this decrease in CI was associated with a significant increase in systemic vascular resistance index (SVRI). Because $\dot{V}_{O_2}$ decreased more than did D_{O_2}, $C(a\text{-}v)_{O_2}$ and the O_2 extraction ratio also decreased, although the only significant change was the oxygen extraction ration for the acute hypothermia animals ($P < 0.05$). Nevertheless, $P\bar{v}_{O_2}$ did not change significantly with cooling. Some volume contraction appeared to be associated with cooling, with a decrease in plasma volume, CVP, and PCWP, and an increase in Hct. However, only the increase in Hct in the acute hypothermia animals was statistically significant ($P < 0.05$).

During the maintenance of hypothermia in the prolonged hypothermia group, $\dot{V}_{O_2}$ and D_{O_2} were consistently reduced from control levels by similar amounts beyond 8 h at 29° C (fig. 1). With this parallel reduction in $\dot{V}_{O_2}$ and D_{O_2}, $C(a\text{-}v)_{O_2}$, O_2 extraction ratios, $P\bar{v}_{O_2}$, pH, and BD were not different from control values. SVRI continued to be significantly above control values.

Acute hypothermia and prolonged hypothermia animals reacted to the rewarming phase of the study differently. Acute hypothermia animals increased $\dot{V}_{O_2}$ to values no different from control, whereas prolonged hypothermia animals had values significantly above control ($P < 0.05$). For both groups D_{O_2} remained significantly below control, although SVRI decreased and CI increased significantly ($P < 0.05$). Thus, for the prolonged hypothermia animals only, $C(a\text{-}v)_{O_2}$ and O_2 extraction ratios increased significantly above control ($P < 0.05$). For both groups of animals, $P\bar{v}_{O_2}$ decreased significantly below control values ($P < 0.05$), although pH and BD did not change significantly. Blood pressure decreased, although no animals in either group required either inotropic drugs or fluid administration to maintain adequate blood pressure.
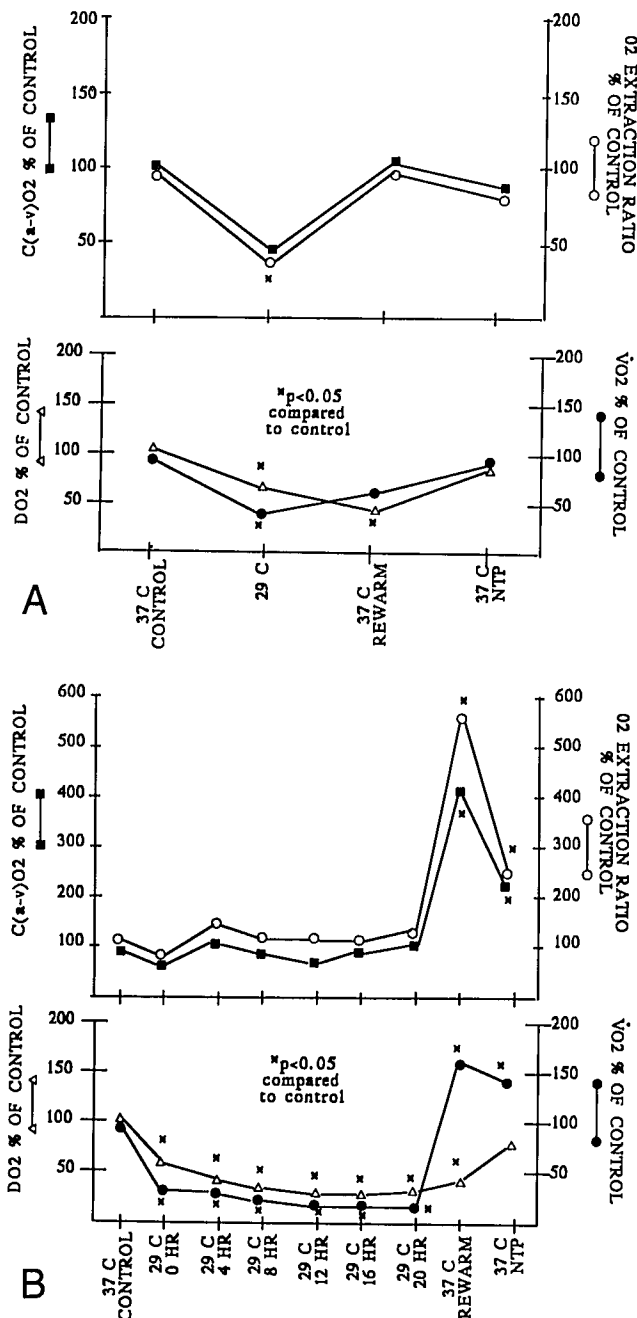
Variable	Group									
Hematocrit	AH	40 ± 6	49 ± 7*	52 ± 8	53 ± 7	50 ± 10	54 ± 8		44 ± 6	
	PH	50 ± 7	54 ± 8	51 ± 5	49 ± 5	52 ± 4	49 ± 8		58 ± 6	
	NC	47 ± 6							46 ± 8	
Pa$_{O_2}$ (mmHg)	AH	414 ± 46	457 ± 88	406 ± 175	419 ± 185	448 ± 208	433 ± 201	503 ± 49	327 ± 163	403 ± 63
	PH	380 ± 182	421 ± 186	390 ± 102	395 ± 107	388 ± 96	374 ± 118		328 ± 150	332 ± 146
	NC	402 ± 83							359 ± 88	
Pa$_{CO_2}$ (mmHg)	AH	39 ± 5	44 ± 7	40 ± 8	40 ± 7	42 ± 7	49 ± 4	49 ± 4	39 ± 3	42 ± 4
	PH	38 ± 11	45 ± 5	37 ± 6	37 ± 4	39 ± 5	38 ± 3		36 ± 7	45 ± 6
	NC	39 ± 4							41 ± 3	
pH	AH	7.30 ± 0.06	7.25 ± 0.06	7.25 ± 0.05†	7.25 ± 0.05†	7.24 ± 0.04†	7.21 ± 0.04†	7.22 ± 0.07	7.30 ± 0.05	7.28 ± 0.02
	PH	7.30 ± 0.07	7.21 ± 0.04	7.37 ± 0.05	7.35 ± 0.03	7.35 ± 0.06	7.36 ± 0.05		7.28 ± 0.05	7.28 ± 0.01
	NC	7.34 ± 0.07							7.33 ± 0.02	
Base deficit (mEq/l)	AH	-6 ± 3	-8 ± 2	-9 ± 2†	-10 ± 1†	-10 ± 1†	-9 ± 2†	-8 ± 4	-7 ± 2	-9 ± 3
	PH	-9 ± 2†	-10 ± 3	-4 ± 1	-5 ± 2	-4 ± 2	-3 ± 3		-9 ± 2†	-6 ± 2
	NC	-4 ± 3							-5 ± 2	

Values are mean ± SD.
AH = acute hypothermia; PH = prolonged hypothermia; NC = normothermic controls;
NTP = sodium nitroprusside.
* $P < 0.05$, versus period 1.
† $P < 0.05$, versus NC.
‡ $P < 0.05$, versus AH and NC.
§ $P < 0.05$, versus period 8.

FIG. 1. Per cent change from control of oxygen delivery ($\dot{V}_{O_2}$), oxygen consumption (D_{O_2}), arteriovenous oxygen content difference ($C(a\text{-}v)_{O_2}$), and O_2 extraction ratio with acute (*A*) and prolonged (*B*) hypothermia and surface rewarming, followed by sodium nitroprusside administration (NTP) in sedated, paralyzed dogs.

The administration of NTP augmented oxygen delivery in both groups of animals but did not have a significant effect on $\dot{V}_{O_2}$. Thus, both $C(a\text{-}v)_{O_2}$ and O_2 extraction ratios decreased in both groups, although these changes were not statistically significant. CI, SVRI, MAP, and $P\bar{v}_{O_2}$ returned to control range with the administration of NTP.

Some of the changes seen in the acute and prolonged hypothermia animals were also seen in the normothermic controls. Following the control period these animals had a significant decrease in D_{O_2}, resulting from a decrease in CI ($P < 0.05$). $\dot{V}_{O_2}$ was unchanged. As a result, $C(a\text{-}v)_{O_2}$ and oxygen extraction ratios were significantly decreased from control values ($P < 0.05$). We suspect that some of the animals may have had increased cardiac output during the control measurements because of instrumentation under light anesthesia despite the time allowed for stabilization thereafter. If so, some, but not all, of the response to acute and prolonged hypothermia may be accounted for similarly.

The normothermic control animals also showed a response to NTP, with a significant increase in D_{O_2} and a decrease in $C(a\text{-}v)_{O_2}$ and oxygen extraction ratio. Thus, the effect of NTP was not specific to animals rewarmed following acute or prolonged hypothermia.

Contraction of plasma volume (PV) was seen in both hypothermic groups, but the change did not reach statistical significance until 20 h in prolonged hypothermia animals. Rewarming resulted in an increase in PV to baseline values. PV did not change in normothermic control animals. The addition of NTP resulted in a significant increase in PV in prolonged hypothermia and normothermic control dogs; the increase in acute hypothermic animals was not statistically significant. Urine output in the prolonged hypothermic animals was higher during the cooling phase ($5.9 \pm 2.4 \; ml \cdot kg^{-1} \cdot h^{-1}$) than during the subsequent 20 h at 29° C ($2.5 \pm 0.7 \; ml \cdot kg^{-1} \cdot h^{-1}$ or during rewarming ($2.0 \pm 1.8 \; ml \cdot kg^{-1} \cdot h^{-1}$) ($P < 0.05$). Urine output during cooling was also higher than that for the normothermic control dogs ($2.9 \pm 0.6 \; ml \cdot kg^{-1} \cdot h^{-1}$) ($P < 0.05$).

Catecholamine concentrations varied widely. Epinephrine concentrations decreased after the control period in all groups, but none of these changes were statistically significant. Norepinephrine concentrations increased during hypothermia, but the changes were not significant. No significant changes in arterial oxygen or carbon dioxide tension were observed in any of the groups during the study period. The prolonged hypothermia animals had a greater baseline base deficit than the other two groups for reasons that are unclear. With cooling both acute hypothermia and prolonged hypothermia animals developed more of a metabolic acidosis than did the normothermic control animals. With rewarming this difference did not persist.

Discussion

In our study the link between oxygen delivery (D_{O_2}) and oxygen consumption ($\dot{V}_{O_2}$) was maintained in dogs subjected to both acute and prolonged (24 h) hypothermia; although $\dot{V}_{O_2}$ decreased more rapidly than D_{O_2} during the cooling phase, both were reduced by a similar

amount after approximately 8 h at 29° C, resulting in no change in tissue oxygen extraction. The response to rewarming, however, was different in the two groups of animals. D_{O_2} failed to keep pace with $\dot{V}_{O_2}$ in both groups, but the discrepancy was larger in the prolonged hypothermia animals because in this group $\dot{V}_{O_2}$ increased above control with rewarming. In both groups of animals NTP administration following rewarming augmented D_{O_2} by increasing cardiac output, indicating a responsiveness of the peripheral vasculature to vasodilation and of the heart to afterload reduction. In the face of increased D_{O_2}, however, $\dot{V}_{O_2}$ did not change, indicating that $\dot{V}_{O_2}$ during rewarming was not supply limited.

Several mechanisms could be invoked to explain the increase in $\dot{V}_{O_2}$ in our prolonged hypothermia animals to values above control during rewarming. Shivering can increase $\dot{V}_{O_2}$ by as much as 600%.[13] However, muscle relaxation was maintained throughout the study period; no animals shivered visibly or had muscle activity artifact seen on ECG.

The increase in $\dot{V}_{O_2}$ to values above control during rewarming in our prolonged hypothermia animals suggests that an oxygen debt had been present that was at least partially satisfied. This debt may have occurred because of severely reduced or absent flow through microvascular channels during prolonged hypothermia. The reduction in plasma volume seen in the animals is consistent with this hypothesis. Using carbon black infusions, Steen et al. observed heterogeneous loss of perfusion to skeletal muscle during prolonged hypothermia in his animals.[6] These areas of decreased or absent perfusion become relatively hypoxic and generate lactate, which because of the perfusion deficit may not reach the central circulation. With reperfusion lactate reenters normal oxidative pathways, consuming oxygen in the process.

Tissue hypoxia also produces adenosine and hypoxanthine as breakdown products of adenosine monophosphate (AMP).[14] With rewarming and reperfusion these compounds can combine with oxygen in the formation of uric acid and oxygen radicals.[14] Thus, nonrespiratory utilization of oxygen may account for some of the increase in $\dot{V}_{O_2}$ observed during rewarming in our prolonged hypothermia animals. The fact that this was not seen during rewarming of the acute hypothermia animals suggests that the perfusion defect is a time-related phenomenon.

Despite the difference in $\dot{V}_{O_2}$ response during rewarming, the acute and prolonged hypothermia groups exhibited a similar decrease in $P\bar{v}_{O_2}$ and increase in oxygen extraction. However, mean $P\bar{v}_{O_2}$ for both groups remained above 40 mmHg and no animal had a significant change in pH or BD. All animals survived the study. This is in marked contrast to the study of Steen et al.,[6] in which all animals had hemodynamic deterioration during rewarming and at least one died. There are a number of possible explanations for the differences in response to

hypothermia and rewarming in the two studies. The lungs of our animals were ventilated with 100% oxygen, whereas those in the Steen et al.[6] study received 30% oxygen. In studies of oxygen transport in hypothermic dogs Bigelow et al.[15] found a lower mortality in animals the lungs of which were ventilated with higher concentrations of inspired oxygen compared with animals the lungs of which were ventilated with room air. The Steen et al.[6] animals had a much higher calculated systemic vascular resistance ($38,743 \pm 9,357$ dyne·s·cm⁻⁵) and much lower cardiac index (approximately 25 ml·min⁻¹·kg⁻¹) than our animals at the end of the hypothermic period. Thus, net oxygen delivery was decreased compared with that in our animals, resulting in a lower $P\bar{v}_{O_2}$ and in the production of a metabolic acidosis not seen in our animals. Others[9,10] have demonstrated a reduction in oxygen extraction with hypothermia. Although the mechanism of reduced efficiency of oxygen extraction during hypothermia remains unclear, reduced capillary blood flow due to an increase in arteriolar and precapillary vasoconstrictor tone has been proposed.[10] All of the Steen et al.[6] animals received high-dose epinephrine infusions (2 $\mu g·kg^{-1}·min^{-1}$) during the warming phase, which could have induced additional vasoconstriction and decreased oxygen delivery. Thus, it seems likely that in the Steen et al.[6] model, reduced inspired oxygen concentration, high afterload, and severely restricted cardiac output resulted in marked reduction of O_2 delivery to some tissues, allowing $P\bar{v}_{O_2}$ to reach the critical value at which lactate production occurs.[16]

A critical level of D_{O_2} is that level below which $\dot{V}_{O_2}$ decreases proportionally to supply.[17] Because the critical level of D_{O_2} depends in part on tissue O_2 requirements, one might expect that hypothermia, by lowering metabolic rate, reduces the critical level of D_{O_2} required to maintain $\dot{V}_{O_2}$. Critical D_{O_2} is not reduced, however, because O_2 extraction is impaired during hypothermia.[9,10] Oxygen extraction has not been evaluated previously during the rewarming phase. During rewarming in our study oxygen extraction increased as $\dot{V}_{O_2}$ increased and D_{O_2} remained below control. This would suggest that increases in oxygen extraction during rewarming are possible, although our study was not designed to test the limits of oxygen extraction by inducing severe reductions in oxygen delivery via hypoxia, severe anemia, or low output.

Much of the increase in systemic vascular resistance that occurs with hypothermia can be accounted for by increases in blood viscosity, which occur from hemoconcentration and from altered rheologic properties of blood at low temperature.[13] Microscopic evaluation of arterioles in hypothermic rat mesentery and hamster cheek pouch have shown reduction and even cessation of flow without a change in the diameter of resistance vessels.[18] Bond et al.[19] observed red blood cell aggregation in dog mesentery during hypothermia. These observations do not rule out

the possibility of active or passive vasoconstriction in other tissues and in other species, however. Local factors, such as a temperature-related decrease in oxygen requirement, could mediate active vasoconstriction[10]; a decrease in plasma volume could cause passive vasoconstriction or "derecruitement" of vessels. It seems unlikely, based on circulating catecholamine levels in our study and others,[20] that catecholamine-induced vasoconstriction is a factor.

Pharmacologic means of improving oxygen delivery during hypothermia and rewarming have not been thoroughly investigated. The administration of pentoxiphylline, a theobromine that increases erythrocyte deformability and reduces resistance to flow in capillaries‡ has been shown to improve oxygen extraction and reduce the critical level of D_{O_2} during hypothermia in dogs.[21] We administered a direct vasodilator, NTP, to determine if the elevated SVRI was pharmacologically reversible and if this would result in increased CI and D_{O_2}. In both acute and prolonged hypothermia animals, NTP resulted in a significant increase in plasma volume, CI, and D_{O_2} and a significant reduction in SVRI. The increment in plasma volume could have resulted from an influx of interstitial fluid or from release of plasma or blood from vessels in which flow had ceased. Intravenous infusion rates were held constant during NTP administration. The significant increase in D_{O_2} associated with NTP administration did not increase oxygen consumption, implying that consumption was not supply-dependent during rewarming. The increase in CI in response to afterload reduction suggests that residual increases in afterload rather than direct myocardial depression were responsible for the low output state. NTP administration following rewarming caused a decrease in the oxygen extraction ratio, reflecting an improvement in delivery relative to consumption. Further studies are required to determine if NTP administration could prevent the severe metabolic acidosis and hemodynamic deterioration observed when O_2 delivery is more limited than in our study.[6]

The results of our study would suggest that with either acute or prolonged hypothermia, $\dot{V}_{O_2}$ and D_{O_2} are reduced by similar amounts; no oxygen deficit occurs unless delivery becomes extremely low, either because of anemia, hemoglobin desaturation, or low output.[6] Given these circumstances, oxygen extraction should increase to compensate but may be limited by changes in regional blood flow.[9,10] With rewarming oxygen debt may occur as $\dot{V}_{O_2}$ increases out of proportion to increases in D_{O_2}. In this setting judicious use of NTP may improve delivery and prevent the onset of oxygen debt.

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‡ Ehrly AM: The effect of pentoxiphylline on the flow properties of human blood. Curr Res Med Opin 5:608–613, 1978

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