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Studies on Bradycardia Mechanism in the Moderately Hypothermic Dog *

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Chronotropic action of isoprenaline on the heart was studied in anesthetized dogs, in euthermic and moderate hypothermic conditions, before and after intravenous administration of atropine and oxprenolol or a cervical bilateral vagotomy. In moderate hypothermia we observed: i) larger duration of the positive chronotropic response to isoprenaline with a delayed and slightly lesser intensity in its maximum; ii) relating to euthermic conditions, delayed but superimposed potentiation of the chronotropic isoprenaline response in atropinized or vagotomized dogs; iii) a small negative chronotropic response to isoprenaline 15 min after oxprenolol, that diminished after atropine; iiii) oxprenolol induced a marked bradycardia nearly twice as intense as in euthermic dogs, almost completely blocked subsequently by atropine. It is concluded that progressive bradycardia in the moderately hypothermic dog is due, among other factors, to a cholinergic action but not to a lesser ability of β-adrenergic cardiac effectors to chronotropic responses.

When both divisions of the autonomic nervous system simultaneously increase their activity the parasympathetic is apparently predominant chronotropically (4, 10, 11). Since the initial works of HOOK and STORMONT (8), CORABOEUF and WEIDMAN (5) and of BRAGANÇA-TENDER *et al.* (1), among others, it has been settled that progressive sinus bradycardia is the earliest and more constant effect of cooling on the heart. This bradycardia has often been ascribed to a specific depression of cardiac tissue by cold (5, 9). This investigation intends to shed additional light on the rôle of the parasympathetic-sympathetic interaction in bradycardia of the moderately hypothermic dog.

Materials and Methods

Mongrel dogs of either sex, weighing between 8 and 16 kg, were used. Animals were anesthetized with sodium pentobarbital (35 mg/kg) intravenously and maintained on artificial respiration through an endotracheal cannula with an open circuit

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pneumatic apparatus. An electric thermocouple cable was placed in the esophagus for continuous body temperature monitoring. Serial lead II electrocardiograms were always recorded. Blood pressure from the cannulated left femoral artery was measured with a mercury manometer and recorded on a smoked kymograph. The left femoral vein was cannulated for drug administration.

Animals were cooled to 31° C in an iced water bath and then removed since temperature continued to fall. In order to maintain the esophagic temperature between 28 and 26° C during all the hypothermic experiments, external heat was applied whenever temperature lowered to 26.5° C.

Isoprenaline, 0.5 μg/kg, was used in all experiments as adrenergic test drug for the chronotropic cardiac response. Parasympathetic cardiac block was achieved at the ganglionar level by bilateral cervical truncus vagotomy, and at the neuro-effector level by atropine, 0.2 mg/kg. The oxprenolol, 0.5 mg/kg, was used as

Table I. *Chronotropic responses to isoprenaline in euthermic and hypothermic dog.* Results are given in seconds as the differences of the mean value of electrocardiographic RR spaces, respectively before and after isoprenaline I.V. injection, at the refered times ± standard deviations. The evaluation of group correlation (8) pointed out significant values between the following correspondent trial groups (for further details, see Methods): I and II; III and IV; V and VI; VII and VIII; and non significant, between IX and X. N = number of experiments. r = correlation coeficient.

Experimental group	Chronotropic effects after Isoprenaline Injection			
	30 s	1 min.	2 min.	3 min.
I. Euthermia N=22 (r=—0.79406)	—0.078 ±0.025	—0.061 ±0.020	—0.026 ±0.023	—0.006 ±0.018
II. Hypothermia N=7 (r=—0.14097)	—0.014 ±0.016	—0.069 ±0.012	—0.051 ±0.015	—0.019 ±0.012
III. Euthermia, 15 min after atropine N=2 (r=—0.98692)	—0.155 ±0.007	—0.120 ±0.000	—0.040 ±0.000	—0.020 ±0.028
IV. Hypothermia, 15 min after atropine N=3 (r=0.57814)	—0.023 ±0.032	—0.100 ±0.020	—0.153 ±0.023	—0.103 ±0.006
V. Euthermia, 15 min after vagotomy N=3 (r=—0.90374)	—0.117 ±0.006	—0.107 ±0.023	—0.067 ±0.023	—0.027 ±0.023
VI. Hypothermia, 15 min after vagotomy N=3 (r=0.61690)	—0.013 ±0.006	—0.067 ±0.012	—0.127 ±0.042	—0.087 ±0.032
VII. Euthermia, 15 min after oxprenolol N=3 (r=—0.40756)	0.000 ±0.000	0.000 ±0.000	—0.003 ±0.006	—0.003 ±0.006
VIII. Hypothermia, 15 min after oxprenolol N=4 (r=0.33791)	+0.015 ±0.013	+0.015 ±0.013	+0.023 ±0.017	+0.028 ±0.022
IX. Euthermia, 35 min after oxprenolol and 15 min after atropine N=3 (r=0.52400)	—0.007 ±0.006	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000
X. Hypothermia, 35 min after oxprenolol and 15 min after atropine N=4 (r=0.17902)	+0.005 ±0.006	—0.003 ±0.005	+0.005 ±0.006	+0.005 ±0.010

β-adrenergic blocker (2,3). All drugs were given intravenously by rapid administration.

The record in seconds of the duration between two successive electrocardiographic R waves, allowed us to express one index of the heart rate. The value considered for the RR space at each instance is the arithmetical mean of those spaces recorded in the E.C.G. during about 5 seconds. Results obtained in each 2 trial protocol correspondent groups, one in euthermia and the other in hypothermia, were subjected to evaluation of groups correlation (6). This analysis was done at the «Authomatic Calculus Center of Oporto University», with the NCR Elliot computer.

Results

Heart rate. In moderate hypothermia, positive chronotropic response to isoprenaline is smaller in its maximum intensity, and more delayed than in euthermic dogs; besides, 15 min. after atropine or a bilateral cervical vagotomy, it undergoes a superimposed potentiation relating to euthermic animals (table I).

Fifteen minutes after oxprenolol injection to euthermic dogs, isoprenaline did not change heart rate even if after atropine. In moderate hypothermia, β-adrenergic blockade by that drug induced a low negative chronotropic effect to isoprenaline, decreasing after atropine (table I).

At least during 10 minutes after intravenous injection of oxprenolol there was a marked negative chronotropic effect, both in euthermia and moderate hypothermia, nearly twice as intense in this last instance. This effect is almost completely blocked subsequently by atropine in the moderately hypothermic animals (table II).

Arterial blood pressure. At euthermic conditions neither atropine nor bilateral cervical vagotomy caused significative changes on the hypotensive responses to isoprenaline.

During moderate hypothermia the mean blood pressure tended to stabilize. At this period, blood pressure responses to isoprenaline showed slight reduction in intensity (fig. 1).

Table II. *Chronotropic responses to oxprenolol and atropine at various thermic conditions.* Results are given in seconds as the differences of the mean value of electrocardiographic RR spaces, respectively before and after exprenolol and atropine I.V. injection, at the refered times±standard deviations. The evaluation of group correlation (8) pointed out significant values between XI and XII groups (for further details, see Methods). N = number of experiments. r = correlation coeficient.

Experimental group	Chronotropic effects after oxprenolol and atropine injection				
	30 s	1 min.	5 min.	10 min.	15 min.
XI. Euthermia, after oxprenolol N=3 (r=0.23235)	+0.083 ±0.031	+0.083 ±0.031	+0.093 ±0.040	+0.100 ±0.040	+0.100 ±0.036
XII. Hypothermia, after oxprenolol N=4 (r=0.68461)	+0.095 ±0.079	+0.173 ±0.072	+0.228 ±0.070	+0.270 ±0.091	+0.340 (*)
XIII. Hypothermia, atropine 20 min after oxprenolol N=4 (r=0.57458)	+0.005 ±0.006	+0.005 ±0.006	+0.013 ±0.015	+0.020 ±0.018	+0.030 ±0.025

(*) Value refered to only one case.

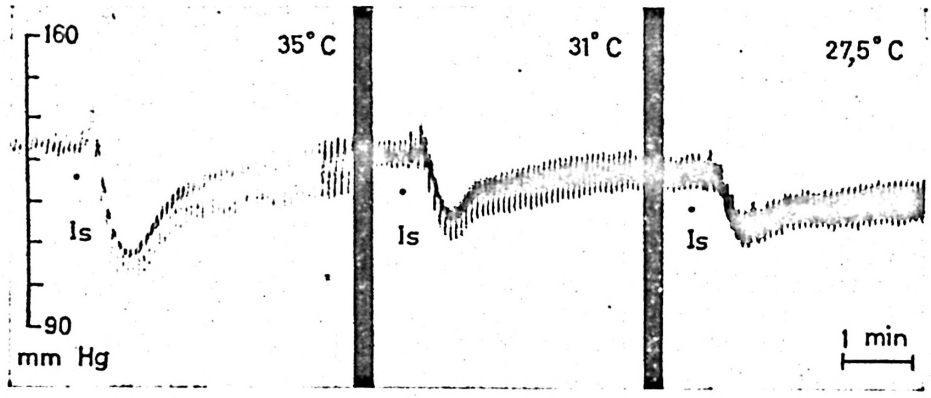

Fig. 1. *Dog (male, 12 kg) blood pressure.*
Each tracing shows the effect of 0.5 μg/kg of isoprenaline (Is) at the various esophagic temperatures indicated.

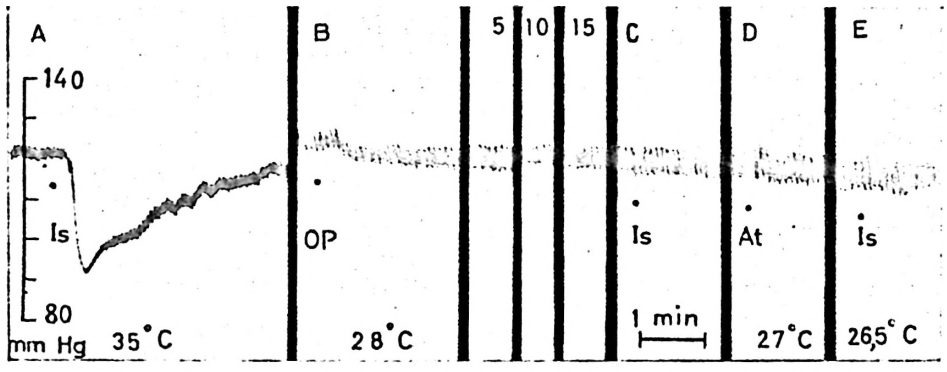

Fig. 2. *Dog (female, 13 kg) blood pressure, during cooling).*
Tracing B shows the acute hypotensive effect of 0.5 mg/kg of oxprenolol (OP). After this drug, isoprenaline (Is) did not allow for any blood pressure effect even after atropine (At). Top tracing numerals indicate time in minutes after β-adrenergic blocker administration. At bottom, values of esophagic temperature.

Figure 2 illustrates the acute hypotensive effect of oxprenolol during moderate hypothermia with subsequent evolution to stabilization. In euthermic dogs, mean blood pressure was back to nearly normal at 5 minutes and was even slightly increased 15 minutes after administration of the drug (fig. 3). The β-adrenergic blockade by this drug in both thermic conditions, did not allow for any blood pressure effect of isoprenaline even after atropine (fig. 2).

Discussion

The superimposed potentiation of the positive chronotropic effect of isoprenaline in moderately hypothermic and euthermic animals, suggest that the β-adrenergic cardiac effectors for chronotropic responses are not significantly affected by the parasympathetic blockade during moderate hypothermia. On the other hand, the slight blood pressure rise 15 minutes after oxprenolol administration to euthermic

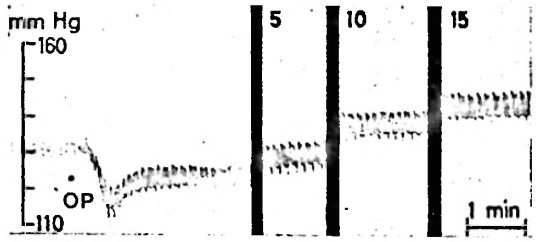

Fig. 3. *Euthermic dog (male, 10 kg) blood pressure.*
Acute hypotensive effect of 0.5 mg/kg of oxprenolol (OP) with recovery by 5 min and a slight increase by 15 min. The numerals indicate time in minutes after injection of this drug.

dogs might mean that, as β-adrenergic blockade is established, α-adrenergic effects with peripheral vasoconstriction become more prominent. The absence of this blood pressure rise in moderate hypothermia is consistent with a decrease of the sympathetic tone in this condition.

Fifteen minutes after oxprenolol injection to euthermic dogs, isoprenaline administration did not change heart rate even after atropine. The β-adrenergic blockade by this drug, apparently induced during hypothermia a low negative chronotropic response to isoprenaline, diminishing after atropine. This can mean that this adrenergic block uncovered not just the «normal» evolution of bradycardia in moderately hypothermic dog but also some negative chronotropic effect of oxprenolol. In fact the administration of oxprenolol alone, induces a marked negative chronotropic effect, nearly twice as intense in hypothermia as in euthermia. In hypothermia, this effect is almost completely blocked subsequently by atropine. These results indirectly support the concept of a significative cholinergic responsibility in the bradycardia recorded after β-adrenergic blockade in moderate hypothermia.

Considering our data as a whole, it appears that progressive bradycardia in moderately hypothermic dog is due, among other factors, to a cholinergic action but not to a lesser ability of β-adrenergic cardiac effectors to chronotropic responses. However, we cannot settle that the cholinergic nervous system prevails over the adrenergic as regards heart rate control, as was demonstrated by SAMAAN (10) for euthermic dog. Considering the extensive interactions of both autonomous divisions of the nervous system (7) and the multiple factors taking place in hypothermia, it may be advanced that only new experimental studies may help to further elucidate participation of these antagonistic systems in this condition.

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Resumen

Se estudia la acción cronotrópica cardíaca de la isoprenalina en perros anestesiados, ya en eutermia ya en hipotermia moderada, antes y después de la inyección por vía venosa de atropina y de oxeprenolol, bien así después de vagotomía cervical bilateral. Se deduce que la bradicardia progresiva en el perro en hipotermia moderada es debida, entre otros factores, a una acción colinérgica y no a una menor capacidad de la respuesta de los efectores adrenérgicos beta cardíacos.

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