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TITLE: INOTROPISM OF MAGNESIUM

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The inotropic effect of magnesium is controversial in human and animal studies[1,2,3]. We evaluated the intrinsic inotropism of magnesium using isolated ventricular septum preparations.

Eight isolated rabbit ventricular septa were studied. Each septum was perfused via its first septal artery with modified Kreb-Ringer-Bicarbonate solution equilibrated with 95% O_2 and 5% CO_2 and maintained at 34°C. The perfusion rate was 1 cc/gm/min. The resting tension was 3-5 gm. Each septum was stimulated supramaximally, 5 volts 5 msec, at 1.7 Hz with a pair of field electrodes. The isometric contraction was stabilized for 30 min before experiment began. At baseline, peak developed tension (T) was more than 2 times the resting tension in each preparation. Magnesium at different concentrations (0, 1.2, 2.4, 5, 10 and 20 mM) perfused the septum for 5 min each at a random sequence. T, +dT/dt, -dT/dt, the time from stimulation to beginning of contraction (Latency), the time from beginning of contraction to peak tension (TPT), and the time duration of isometric relaxation of half the developed tension ($RT_{½}$) were measured. Complete recovery was reached between perfusates. Data (mean ± SD) were analyzed with repeated measures ANOVA and Dunnett's contrast for p less than 0.05.

The results demonstrated that magnesium depressed the contractility, prolonged the latency, and shortened the TPT at 20 mM, but did not affect the $RT_{½}$. (Table)

Magnesium causes a direct myocardial depression only at high concentrations. The attenuated T along with a prolonged latency and a shortened TPT implicates that magnesium inhibits the calcium influx, decreases the calcium availability to the contractile proteins, or competes with calcium at the contractile site. Although magnesium decreases -dT/dt, it does not shorten $RT_{½}$. Therefore, the clearance of calcium away from the contractile components is also inhibited by magnesium. In summary, magnesium at high concentration depresses myocardial contractility and slows myocardial relaxation.

References

1. Eur J Pharmacol 165:181-189, 1989
2. Anesthesiology 73:A282, 1990
3. Clin Cardiol 11:541-545, 1988

TABLE 1. Maximal developed tension (T), maximal differentiation of tension (+dT/dt, -dT/dt), latency, time to peak tension (TPT), and half relaxation time (RT1/2) of myocardium during magnesium perfusion. (n=8)

	Mg (mM)				
	0	1.2 (control)	5	10	20
T (%)	100±2	100	99±3	98±3	82±5*
+dT/dt (%)	101±4	100	100±3	99±4	81±4*
-dT/dt (%)	97±4	100	98±4	91±3*	74±4*
Latency (msec)	23±4	23±4	22±4	25±5	28±4*
TPT (msec)	145±7	148±4	144±7	142±8	138±2*
RT1/2 (msec)	105±6	103±6	102±6	101±7	105±7

*p<0.05 compared with control
Mean ± (SD)

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TITLE: AGING AFFECTS KINETIC ESTIMATES OF VOLUMES AND PERFUSIONS FOR VOLATILE ANESTHETICS IN HUMANS

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Changes in cardiac output, lean body mass, and fat body mass due to aging suggest the possibility that aged patients may differ from young patients in the way they eliminate volatile anesthetics. To investigate the possibility that aging affects the kinetics of volatile anesthetics, we studied 7 young patients (24-37 years) and 11 aged patients (59-87 years) who underwent uneventful abdominal surgeries. We obtained prior approval from the Committee on Human Research at the University of California at San Francisco and written informed consent from each patient. Isoflurane (0.37 ± 0.01%), enflurane (0.57 ± 0.02%), halothane (0.23 ± 0.01%), and methoxyflurane (0.07 ± 0.01%), were administered simultaneously. Anesthetic concentrations in end-tidal and mixed expired gases were measured during 30 min of administration and during 5-7 days of elimination. Mammillary rate constants were determined using a five cpt mammillary model fit simultaneously to the logarithm of the concentration of anesthetics in the end-tidal and mixed expired gas. We used these mammillary rate constants to estimate tissue perfusion and tissue volume for each kinetically defined cpt. For this calculation, we speculated on the physiological identity of each kinetic cpt. We assumed that the 1st cpt represents lung tissue, the 2nd and 3rd cpts represent vessel-rich group and muscle group, respectively, and the 4th and 5th cpts represent fat. To estimate perfusion to each cpt we multiplied the corresponding mammillary rate constant by the corresponding tissue/blood partition coefficient and by 100. To estimate tissue volume we multiplied the volume of the central cpt (V1) by the ratio of the corresponding ingress and egress mammillary rate constants for each cpt and divided the result by the tissue/gas partition coefficient appropriate to each tissue. Volume of distribution at steady state was also determined from the mammillary rate constants.

Perfusion estimates for the 2nd cpt decreased with age for all 4 anesthetics ($p = 0.01$-0.14; r^2 = 15-28%) but reached statistical significance for only the 3 insoluble anesthetics isoflurane, enflurane, and halothane ($p \leq 0.05$; r^2 = 18-28%). Perfusion estimates decreased with age for all 4 anesthetics for the 4th and 5th compartments ($p = 0.01$-0.25; r^2 = 5-32%), but reached statistical significance ($p \leq 0.05$) for only the 2 less soluble anesthetics, isoflurane and enflurane for the 5th cpt. Volume estimates for the 4th and 5th compartments increased with age for all 4 anesthetics ($p = 0.01$-0.25; r^2 = 5-32%) but this trend only reached statistical significance ($p \leq 0.05$) for isoflurane and enflurane (4th cpt) and halothane (5th cpt). The apparent volume of distribution at steady state increased with age for all 4 anesthetics ($p = 0.04$-0.20; r^2=9-23%).

Our data suggest that aging is accompanied by increased body fat (4th and 5th cpts) and decreased perfusion to the vessel-rich and fat groups (2nd and 5th cpts). We conclude that although aging affects kinetic estimates of tissue perfusions and volumes, the effects are small and unlikely to affect clinical practise in normal patients.

Mean Perfusions (ml/100 ml tissue volume/min)

Cpt	Isoflurane (n=11)	Enflurane (n=11)	Halothane (n=9)	Methoxyflurane (n=7)	Literature
	Age 73.2 ± 3.1 yr		Weight 72.7 ± 3.1 kg		
2	30.06 ± 2.15[a]	24.26 ± 1.85[b]	23.78 ± 2.61[c]	11.21 ± 1.18	60.7
3	3.07± 0.50	2.04± 0.24	3.33 ± 1.06	4.14 ± 1.19	2.5
4	11.79 ± 1.41	9.05 ± 1.18	15.25 ± 2.19	14.04 ± 3.28	--
5	1.63± 0.12[d]	1.44± 0.10[e]	2.02 ± 0.24	1.81 ± 0.32	2.4
	Age 31 ± 1.8 yr		Weight 65.2 ± 3.0 kg		
Cpt	(n=7)	(n=7)	(n=7)	(n=4	
2	42.20 ± 2.80[a]	31.92 ± 2.97[b]	37.03 ± 4.69[c]	15.28 ± 2.38	60.7
3	3.16± 0.17	2.25± 0.11	3.76 ± 1.11	3.85 ± 0.87	2.5
4	16.18 ± 1.94	11.27 ± 1.18	22.31 ± 5.00	20.66 ± 6.96	--
5	2.87 ± 0.54[d]	2.37 ± 0.38[e]	2.85 ± 0.53	2.30± 0.46	2.4

[a, b, c, d, e] Pairs of values are statistically different ($p \leq 0.05$).

Mean Compartmental Volume (liters)

Cpt	Isoflurane (n=11)	Enflurane (n=11)	Halothane (n=9)	Methoxyflurane (n=7)	Literature
	Age 73.2 ± 3.1 yr		Weight 72.7 ± 3.1 kg		
2	3.93 ± 0.45	3.68 ± 0.40	3.44 ± 0.45	3.04 ± 0.55	3.6
3	14.56 ± 2.24	18.41 ± 2.46	10.32 ± 2.09	4.84 ± 1.59	23.4
4	3.33 ± 0.46	3.55 ± 0.45[f]	1.39 ± 0.24[h]	0.64 ± 0.11	--
5	15.92 ± 2.14	14.85 ± 2.01	9.59 ± 1.16[g]	5.24 ± 1.10	13.5
	Age 31 ± 1.8 yr		Weight 65.2 ± 3.0 kg		
Cpt	(n=7)	(n=7)	(n=7)	(n=4)	
2	3.93 ± 0.30	3.88 ± 0.41	3.64 ± 0.53	3.67 ± 0.53	3.6
3	12.20 ± 1.19	17.41 ± 1.53	7.99 ± 1.36	2.86 ± 1.08	23.4
4	2.01 ± 0.33	2.40 ± 0.35[f]	0.90 ± 0.17[h]	0.45 ± 0.11	--
5	9.74 ± 3.27	9.53 ± 3.42	5.09 ± 1.70[g]	3.36 ± 1.27	13.5

[f, g, h] Pairs of values are statistically different ($p \leq 0.05$).
Values are mean ± SEM.