Variation in Serum Ionized Calcium on Cardiopulmonary Resuscitation

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Changes in serum ionized calcium (Ca^{++}) levels during cardiopulmonary resuscitation (CPR) and before and after $CaCl_2$ administration have been examined and investigated in 30 patients with cardiopulmonary arrest on arrival (dead on arrival patients) when a significant negative correlation was found to exist between the transportation time and aCa^{++}, as the aCa^{++} level decreased with an increase in the transportation time. Upon arrival, the pH had fallen due to acidosis so that aCa^{++} and cCa^{++} levels were virtually normal. After admission, the pH rose as a result of CPR, resulting in a significant drop in both Ca^{++} levels, so that in most cases resuscitation was not possible. Those successfully resuscitated took over 60 min to return to normal Ca^{++} levels. Administration of approximately 6.6 mg/kg of $CaCl_2$ led to significant increases in aCa^{++} and cCa^{++} to essentially normal levels, even with some patients recording extremely elevated Ca levels, even with some patients recording extremely elevated Ca levels. However, the success rate of resuscitation was not found to show any significant difference according to whether $CaCl_2$ had or had not been administrated.

Thus, it is felt neccessary to re-examine the use of calcium chloride on CPR.
(Key words: serum ionized calcium, cardiopulmonary resuscitation)

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Calcium (Ca) plays an important role in the contraction and stimulation of the myocardium. However, its use in cardiopulmonary resuscitation (CPR) is in dispute. The 1986 edition of the Standards and Guidelines for CPR and ECC (CPR and ECC[1]) put limitation on the use of calcium and the dosage recommendations also have been changed. All data on the variation of Ca levels upon CPR are based exclusively on animal experiments conducted with dogs[2] and no data from actual CPR-related Ca changes on humans are available. This has prompted the authors to measure and examine the changes in serum ionized Ca (Ca^{++}) during CPR as this form of Ca is believed to be the best indicator of the patient's physiological activity among the three forms of Ca occurring in the body, i.e., protein binding Ca, complex Ca, and Ca^{++}. The results of these measurements have been analyzed and are reported below.

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Subjects and Methods

The subjects of this study were 30 dead-on-arrival (DOA) patients with cardiopulmonary arrest due to internal factors. These subjects were obtained by excluding infants and patients with trauma brought to the

Table 1. Measurements performed on arrival

		Age (years)	Transportation time (min)	Total protein (mg/dl)	PH	Ca (mg/dl)	cCa^{++} (mEq/L)	aCa^{++} (mEq/L)
All Pt (n = 30)		55.5 ± 17.9	23.9 ± 8.9	6.24 ± 0.81	7.096 ± 0.19	9.33 ± 0.92	2.24 ± 0.18	2.33 ± 0.18
I	Res (+) (n = 16)	57.9 ± 16.7	21.2 ± 7.7	6.24 ± 0.72	7.137 ± 0.13	9.04 ± 0.75	2.28 ± 0.16	2.36 ± 0.18
	Res (−) (n = 14)	52.7 ± 19.4	27.0 ± 9.5	6.23 ± 0.93	7.049 ± 0.24	9.66 ± 1.00	2.20 ± 0.18	2.31 ± 0.19
		NS	NS	NS	NS	NS	NS	NS
II	Res (+) (n = 12)	57.4 ± 17.6	21.0 ± 8.6	6.29 ± 0.82	7.113 ± 0.06	8.92 ± 0.74	2.28 ± 0.18	2.36 ± 0.19
	Res (−) (n = 7)	52.8 ± 16.7	30.0 ± 11.7	5.85 ± 0.59	7.036 ± 0.28	9.71 ± 0.96	2.14 ± 0.15	2.25 ± 0.18
		NS	NS	NS	NS	NS	NS	NS

(Mean ± SD)

Res; Resuscitation, NS; Not Significant, I; Patients treated with or without calcium, II; Patients treated without calcium

hospital dead on arrival. The patients' average age was 55.5 ± 17.9 years and the sex breakdown 23 males and 7 females. Administration of a 2%$CaCl_2$ solution was used on 11 of these patients, and 16 patients were resuscitated. The time gap from notifying the rescue team to the patients' delivery to the hospital was 23.9 ± 8.9 min, with basic life support having been tried on all of the patients.

Immediately after transportation, a blood sample was taken by direct puncture of the femoral artery. The blood sample was assayed for Ca^{++}, total Ca, blood gases, and total protein. Taking blood samples were subsequently attempted at 15 min intervals by using an indwelling catheter in the femoral artery measuring the arterial blood pressure. Those patients who respond to the resuscitation had four blood samples and those who did not respond to the resuscitation treatment had two blood samples taken to determine Ca^{++} and blood gas. Ca^{++} assay was carried out by the ion electrode method (SERA 250 manufactured by Horiba), using the serum. Immediately after blood sampling the sample was injected into a sealed and dry test tube filled to over 85% with blood. After storage at 4°C for approx. 15–20 min, the sealed test tube was placed in a centrifuge for centrifugal separation of the serum which was subsequently stored deep-frozen and assayed. The assay result was determined as the corrected Ca^{++} (cCa^{++}) at pH 7.40 calculated from the equation:

$$\log Ca^{++} \text{ (at pH 7.40)} = \log Ca^{++} \text{ (at pH measured)} + 0.14 \text{ (pH} - 7.40) \quad (1)^3$$

(with normal value being 2.24–2.58 mEq/L). mEq/L). From this value, the actual Ca^{++} (aCa^{++}) level was calculated at the patient pH from the equation:

$$\log Ca^{++} \text{ (at pH 7.40)} = \log Ca^{++} \text{ (at patient pH)} + 0.14 \text{ (pH} - 7.40) \quad (2)$$

and the approximation equation:

$$cCa^{++} = aCa^{++} + 0.14 \text{ (pH} - 7.40) \quad (3)$$

All assay data were stated in terms of mean ± standard deviation, unless where impracticable. These results were statistically treated by using the F-test, Student t-test and x^2 test. A significant difference was considered to exist of $P<0.05$.

Results

1. Measurements performed on arrival

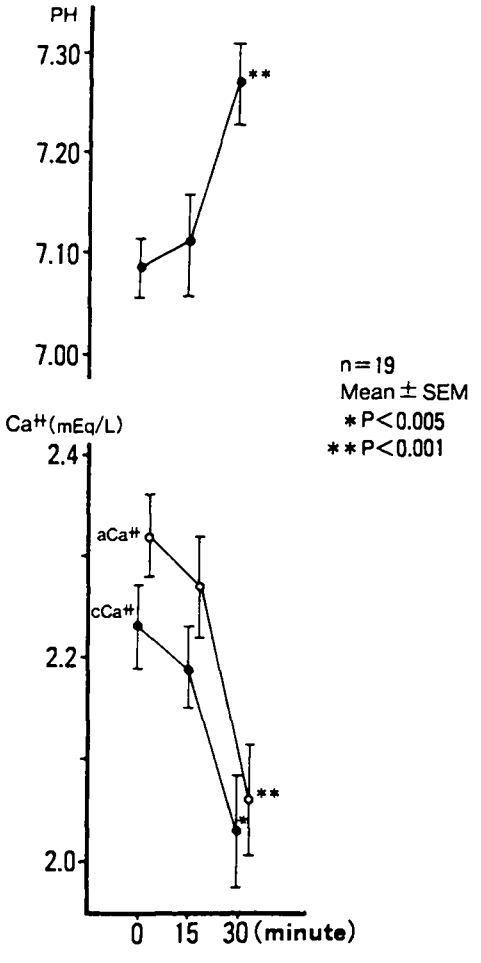

Fig. 1. Post-Arrival changes in PH, aCa^{++}, and cCa^{++} of those treated without $CaCl_2$.

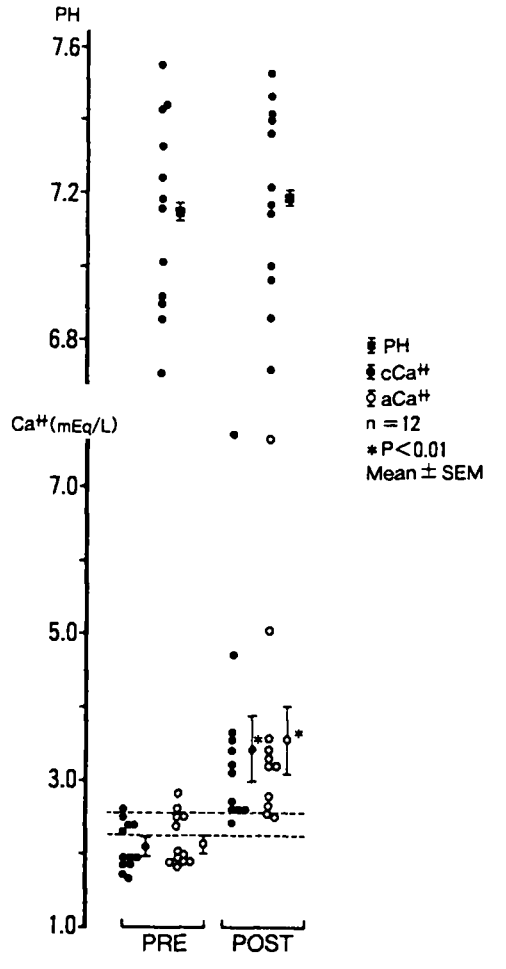

Fig. 2. Changes in PH, aCa^{++}, and cCa^{++} before and after $CaCl_2$ administration.

(table 1)

The tortal protein and tortal Ca levels were generally normal. Measurements showed a significant drop in pH due to acidosis, while both aCa^{++} and cCa^{++} were virtually within the normal range. Group I included all of the DOA patients and was divided into resuscitation positive and negative subjects, and for this group it was not possible to find a significant difference. However, the resuscitation negative subjects tended to report low pH, aCa^{++} and cCa^{++} levels, and their transportation time also tended to be long. Group II consisted of patients not treated with calcium chloride and was divided into resuscitation positive and negative subjects, and it was found that this group showed virtually the same tendencies as the former group.

2. Post arrival changes in pH, aCa^{++}, cCa^{++}

The 19 subjects of the non-$CaCl_2$ treated group were examined to determine the changes in pH, aCa^{++}, and cCa^{++}, by taking the measurements on arrival as the control (fig. 1). As shown in figure 1, while pH showed a significant rise with values of 0; 7.084 ± 0.17, 15; 7.114 ± 0.22, 30; 7.270 ± 0.18 ($P<0.001$), but acidosis had still continued. The values for cCa^{++} were: 0; 2.23 ± 0.18, 15; 2.19 ± 0.21, 30; 2.03 ± 0.28 mEq/L ($P<0.005$), and those for aCa^{++}: 0;

Table 2. Measurements of 19 subjects treated without calcium, who was divided into two sub-groups according as to whether they responded positively or negatively to resuscitation

	Time (min)	0	15	30	45	60
PH	Res (+)	7.113 ± 0.06	7.162 ± 0.18	7.346 ± 0.12***	7.372 ± 0.13***	7.362 ± 0.15***
	Res (−)	7.036 ± 0.28	7.031 ± 0.27	7.139 ± 0.22	–	–
cCa^{++} (mEq/L)	Res (+)	2.28 ± 0.18	2.17 ± 0.14*	2.11 ± 0.13**	2.13 ± 0.15*	2.22 ± 0.19*
	Res (−)	2.14 ± 0.15	2.21 ± 0.31	1.90 ± 0.42	–	–
aCa^{++} (mEq/L)	Res (+)	2.36 ± 0.19	2.24 ± 0.18*	2.12 ± 0.14***	2.13 ± 0.14***	2.23 ± 0.20*
	Res (−)	2.25 ± 0.18	2.32 ± 0.36	1.95 ± 0.40	–	–

(Mean ± SD)

Res; Resuscitation (+): n = 12
Res; " (−): n = 7
*; $P<0.05$, **; $P<0.005$, ***; $P<0.001$ vs control (0 min)

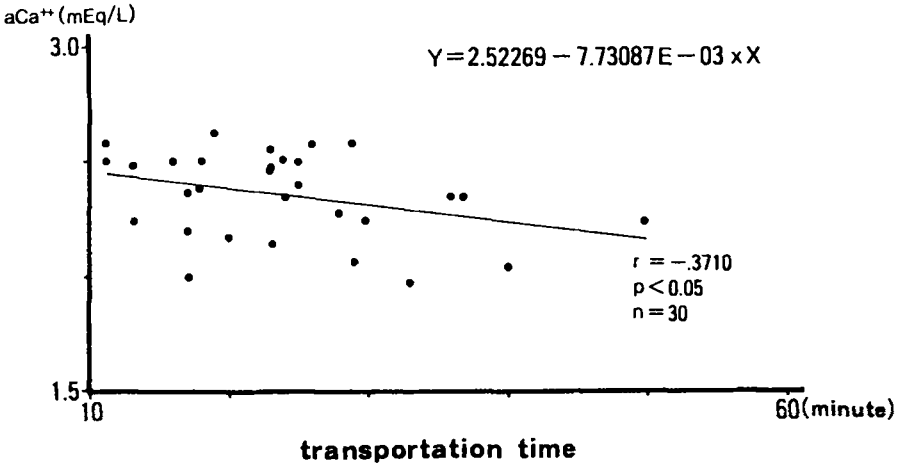

Fig. 3. Correlation between the transportation time and the aCa^{++} level.

2.32 ± 0.19, 15; 2.27 ± 0.25, 30; 2.06 ± 0.27 mEq/L ($P<0.01$), thus showing a significant drop after 30 min. This group of 19 subjects were divided into two sub-groups according as to wheather they responded positively or negatively to resuscitation and the resuscitation positive and negative patients were compared. The measurement results for the resuscitation positive patients were examined, with the values on arrival as the control parameter (table 2). The resusitation negative group tended to show lower values for all of the three parameters, i.e., pH, aCa^{++}, cCa^{++}. The pH of the resusitation positive patients had risen significantly after 30 min and were within normal range. Both aCa^{++} and cCa^{++} dropped significantly after 15 min reaching a minimum at 30 min and tending to show a gradual rise after 30 min. But after 60 min, the aCa^{++} and cCa^{++} levels had not recovered to the normal values.

3. Changes in pH, aCa^{++}, and cCa^{++} before and after $CaCl_2$ administration (fig. 2)

Intravenous injection of 20 ml of 2%$CaCl_2$ solution was administered a total of 12 times (approximately 6.6 mg/kg on the basis of an estimated average body weight 60 kg),

followed by blood smapling roughly 5–10 min after each injection. The pH measurements were: pre-injection: 7.146 ± 0.26, post-injection: 7.118 ± 0.25, with no significant difference between pre- and post-injection pH being detectable. cCa^{++} value were: pre-injection: 2.08 ± 0.32, post-injection: 3.45 ± 1.48 mEq/L ($P<0.01$) and aCa^{++} levels were: pre-injection: 2.15 ± 0.37, post-injection: 3.54 ± 1.45 mEq/L ($P<0.01$). This shows that Ca levels rose significantly above the normal levels after administration of $CaCl_2$. Two patients recorded an extremely sharp rise in cCa^{++} and aCa^{++} from 1.85 to 5.00 and from 2.37 to 7.62 mEq/L, respectively.

4. *Transportation time vs. aCa^{++} and $CaCl_2$ vs. resuscitation success rate (fig. 3)*

The transportation time and the aCa^{++} level at the time of arrival revealed a significant negative correlation ($P<0.05$). No difference in the resuscitation success rate was detected according as to whether $CaCl_2$ had been administered or not.

Discussion

Ca^{++} is susceptible to changes in pH, and through the addition of acid, base, and CO_2 to the serum, Schwartz[4] and Lindgärde[5] have linear relationship between pH and $logCa^{++}$ at pH 7.0 – 8.0 and pH 6.7 – 8.5, respectively and calculated cCa^{++} at pH 7.46, 7.41, by using a correction factor of 0.30 and 0.297, respectively. The equation (eq. 1) used here was established on the basis of ambient temperature exporsure[3] and gives a linear relationship at pH 7.40 – 7.90. However, the authors have extended the use of this formula on the assumption that it can also be applied below pH 7.40. The correction formula assumes that it is not subject to any distorting effects due to age, hematcrit, and albmin[3]. The assaying equipment permitted simaltaneous cCa^{++}, sample Ca^{++}, sample pH measurement. We conducted the blood sampling, separation and assaying procedures under virtually anaerobic conditions to minimize changes in pH, but sample Ca^{++} and aCa^{++} are believed to be dissociated so that the aCa^{++} level was calculated with equation (2) and (3) on the basis of the blood gas assay conducted at the same time.

It is general knowlege that Ca^{++} plays an important role as an intracellular transmitter substance in connection with the exitation – contraction coupling of the myocardium, and its use has thus also been recommended in CPR[6]. However, Ca is also reported to be effective in electromechanical dissociation (EMD)[7,8], although retrospective[7,9] and prospective rondomized double-blind studies[10] appear to deny the effectiveness of $CaCl_2$ in cardiac arrest. According to some reports[2,11], the concentration of Ca in the blood is said to reach danger levels upon administration of $CaCl_2$, and the 1986 edition of CPR and ECC[1] limits the use of calcium preparation in CPR and reduces the dosage levels. There are also arguments to the contrary[12], with certain reports claiming that the use of Ca channel blockers to inhibit the influx of Ca into the cell, triggered as a result of ischemia-induced ATP depletion, is an effective means of achieving cerebral resuscitation[13,14] and of preventing damage to the myocardial cells[15,16]. This shows that the use of calcium preparations in CPR is a matter of great controversy. Yet, the only existing literature reference is the report by Best[2] et al. on Ca^{++} changes in CPR which is based on dog experiments, and this is the first report referring to research concerning the Ca^{++} changes taking place during actual CPR.

This study has shown that the drop in aCa^{++} is proportionate to the transportation time and that with the commencement of post-transportation advanced life support, a significant drop takes place, with the patients successfully reponded to resuscitation taking over 60 min to regain normal levels. And the patients incapable of resuscitation tended to show a more noticeble drop in Ca^{++}. Many patients recorded a significant rise in Ca^{++} to above-normal and even to a danger level after $CaCl_2$ administration. The results reported by Best[2] et al. are in contradiction to those found by the authors of this study. This is due to the fact

that Best et al. refer to CPR under conditions significantly different from practical reality by maintaining blood pressure with 5 μg/kg/min epinephrine after cardiac arrest during a period of 5 min, without any record of pH, aCa^{++}, and cCa^{++} having been taken.

The reason why Ca^{++} drops during CPR is attributed to various factors such as shock-induced intracellular Ca^{++} transfer, suppression of the parathormone (PTH) reaction, inadequate Ca release from the bones due to a reduced blood flow, a drop in Mg, and reduced phosphate excretion due to abated renal function[17–20]. The changes in pH are consequent upon these actions. It has been reported[13–16] that, as pointed out earlier, the use of Ca channel blockers is an effective means of preventing cerebral and myocardial cell lesions due to Ca^{++} influx into the cell. This approach has also been reported[20,21] as being effective in hemorrhagic shock. However, Lucas[19] et al. have found that drop in Ca^{++} and a rise in PTH occur simultaneously after hemorrhagic shock and emphasizes that the rise in PTH can be interpreted as a physiological reaction designed to protect the body while the adjustment of the Ca^{++} level is effective, if the PTH release is not definite as is the case in real-life shock conditions and if Ca^{++} separation is not assured with certainty due to a reduced blood flow to the bones, although a PTH release takes place. In our present study, the use of $CaCl_2$ was not found to have an effect on the resuscitation success rate. When attempt were made to normalize the pH, the Ca^{++} level paradoxically was seen to fall below normal values, a fact which was particularly in evidence in the resuscitation negative patients. And it can not currently be demonstrated that the use of Ca channel blockers in CPR is definitely effective[12]. Thus, in addition to the amendments made in the current 1986 edition of CPR and ECC[1], it is considered meaningful to use Ca to strengthen the myocardial contraction in whom no reaction with other cathecolamines takes place after the resumption of blood circulation, following a long transportation time and EMD[7,8]. There may therefore be some further scope for reconsidering the use of Ca preparations in CPR.

The $CaCl_2$ dosage used in this study was approximately 6.6 mg/kg and therefore corresponded to the dosage recommended in the 1980 edition of CPR and ECC[6]. In many cases, it was found that, similarly to other reports[2,11], the Ca^{++} levels rose to such an extent that dangerously high levels were reached. The 1986 edition of CPR and ECC[1], however, has halved this dose, a step felt appropriate in the light of our present results. If neccessary repeated administration be applied, however, the present study has shown that Ca^{++} levels remain high even after 10 min of administration when blood sample were taken. This apperes to suggest that if repeated administrations are required, these should be performed at intervals of at least 10 min or longer and by halving the dosage on successive administration.

The purpose of the present study referring to 30 DOA patients has been to investigate the changes in Ca^{++} associated with CPR, and the results have confirmed that Ca^{++} decreases with CPR.

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