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Level of Serum Ionized Calcium in Severe Injury : Clinical and Experimental Study

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Recent studies have shown that the rapid inflow of serum ionized calcium (iCa^{2+}) into cells may be the main cause of cell damage and apoptosis in shock, tissue ischemia, and reperfusion. Since patients with serious trauma are often associated with shock and respiratory failure leading to tissue ischemia, reduced serum iCa^{2+} after being injured may be useful for predicting the severity, urgency, and prognosis of patients with trauma. The intracellular inflow of serum iCa^{2+} was reported to activate constitutive nitric oxide synthase (cNOS), which is an invasion mediator. This study measured serum iCa^{2+}, tissue NO, and inflammatory cytokines interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), and examined histopathological samples in an experimental rat model of heavy bleeding, in order to determine if heavy bleeding, a major morbid state of serious trauma, influenced the measurements of serum iCa^{2+}, tissue NO, IL-8, and TNF-α. This study also measured serum iCa^{2+} in emergency patients with trauma on admission and through the subsequent hospitalization period to examine its relationship with other indicators including trauma severity score (ISS), time from being injured to arrival, presence of shock, blood gas findings, clinical course, and prognosis, thereby evaluating the diagnostic and therapeutic importance of serum iCa^{2+}. The results with the experimental rat model of heavy bleeding showed serum iCa^{2+} lowered significantly and IL-8 and TNF-α increased significantly after 30% of the whole blood was exsanguinated, and that tissue NO tended to increase over time. The results from patients with trauma showed serum iCa^{2+} lowered in serious cases leading to death and those with high ISS, heavy bleeding, shock, and metabolic acidosis. These results indicate that serum iCa^{2+} can be a useful indicator for predicting severity, reaction to treatment, and trauma prognosis.

Introduction

Intracellular calcium plays an important role in maintaining cellular functions. Serum ionized calcium (iCa^{2+}) with physiological activity is regulated to a narrow range of 1.12 to 1.30 mmol/L by the endocrine system[1]. A recent study has revealed that the rapid intracellular inflow of serum calcium may be a main cause of cellular damage

and apoptosis from shock, tissue ischemia, and reperfusion[2]. Since patients with serious trauma develop shock and respiratory insufficiency leading to tissue ischemia, the reduced serum iCa^{2+} after injuries may be useful for predicting the severity, urgency, and prognosis of patients with trauma. Another study has reported that cNOS, a NO synthase that mediates invasion, is activated by the intracellular inflow of serum iCa[3].

This study was designed with the following objectives:

1) Histopathological images were examined in a rat model of heavy bleeding, serum iCa^{2+}, and tissue nitric oxide NO, and, at the same time, interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), which are inflammatory cytokines, were also examined in order to determine whether heavy bleeding, a main morbid state of severe trauma, influences serum iCa^{2+}, tissue NO, IL-8, TNF-α, and organs.

2) Serum iCa^{2+} in emergency patients with trauma was measured on their arrival at the hospital and during their subsequent hospitalization periods in order to examine its relationship with indicators such as trauma severity score (ISS), time from injury to arrival at the hospital, shock, blood gas findings, clinical course, and prognosis, thereby evaluating the diagnostic and therapeutic importance of serum iCa^{2+} in patients with trauma.

Materials and Methods

The control and treatment of experimental animals for this study was approved by the Institutional Committee of Fukui Medical University.

1. Experimental subjects and methods

Twelve male Sprague-Dawley (SD) rats with body weight from 350 g to 450 g purchased from Clea Japan Inc. (Jcl: SD Retire) were used for the experiment. A polyethylene tube (PE50 tube) was placed in the left cervical artery under anesthesia with sodium pentobarbital (50 mg/kg, ip) to exsanguinate blood and collect blood samples. At the same time, the abdomen was opened to place a fine NO electrode (φ200 μm; Intermedical Corp, Nagoya) on the renal outer membrane, which was used to measure tissue NO.

The following experiment was performed after 24 hours to avoid the effect of the surgical pretreatment on the experimental results. At first, blood samples were collected from the cervical artery for all the animals and considered as controls. Immediately after that, 20% (n=6) and 30% (n=6) of the estimated amount of the whole blood (8% of body weight) was exsanguinated in 15 minutes. Blood samples were collected again from the 20% and 30% exsanguination groups 3 hours after the completion of the exsanguination. Serum iCa^{2+}, IL-8 and TNF-α by measurement kit, EIA method PRF081 (Panapharm Laboratories Co. Kumamoto) were measured in both groups to compare the results. At the same time, the renal fine NO electrode was used to record the change in the tissue NO production in real time[4)5)].

2. Clinical patients and methods

The subjects were 256 emergency patients with trauma who arrived by ambulance at the emergency room of Fukui Medical College from January 1997 to December 1998. The patients who arrived at the emergency room and died there were excluded. The patients were 185 males and 71 females with a mean age of 47.7 ± 24.2 years. The most frequent cause of trauma was traffic accidents in 184 cases (72%), followed by tumbling in 31 cases (12%) and falling in 25 cases (9.7%). Seventeen patients died after they were hospitalized, and 15 of them died in less than 2 days after admission. The causes of death included hemorrhagic shock in 11 cases, head trauma in 2, and suffocation in 2. The remaining 2 patients died in less than 3 months after admission: one from cerebral death and the other from

Table 1 Difference in serum iCa^{2+}, IL-8, TNF-α in rat heavy hemorrhagic model

	Control group (n=12)	20% exsanguination group (n=6)	30% exsanguination group (n=6)
iCa^{2+} (mmol/L)	1.326±0.006	1.310±0.012	1.220±0.015**
IL-8 (ng/mL)	0.23±0.19	0.21±0.03	0.48±0.05*
TNF (pg/mL)	<16.0	<16.0	26.83±3.94*

*p<0.05, **p<0.01.

multiple organ failure.

The 256 subjects were divided into the deceased group of 17 patients and the surviving group of 239 patients to compare their serum iCa^{2+} on arrival, ISS, time from being injured to arrival, presence of shock (maximum blood pressure of 80 or lower) on arrival, and base excess (BE). The 239 surviving patients were subdivided into 2 groups consisting of 29 patients with serum iCa^{2+} of less than 1.12 mmol/L (low iCa^{2+} group) on arrival and 210 patients with normal serum iCa^{2+} of 1.12 to 1.30 mmol/L (normal iCa^{2+} group) to compare ISS, presence of shock on arrival, and BE. The change in serum iCa^{2+} during the hospitalization period was investigated in some patients by measuring it with i-STAT (Fuso Chemical Industries, Kanazawa).

For statistical processing, Student's t-test was used to test significant differences between the 2 groups, with a probability level of less than 0.05 being considered significant. All data were shown as mean ± standard deviation.

Results

1. Experimental results

Serum iCa^{2+} was 1.326 ± 0.006 and 1.310 ± 0.012 mmol/L in the control (n=12) and 20% exsanguination groups (n=6), respectively. No significant difference in serum iCa^{2+} was observed between the 2 groups, although it was slightly lower in the latter group. It was significantly lower, however, at 1.220 ± 0.015 mmol/L in the 30% exsanguination group (n=6). The serum IL-8 and TNF-α measured at the same time were 0.23 ± 0.19 ng/mL and <16.0 pg/mL in the control group and 0.21 ± 0.03 ng/mL and <16.0 pg/mL in the 20% exsanguination group, respectively, with no significant difference. In contrast, they were 0.48 ± 0.05 ng/mL and 26.83 ± 3.94 pg/mL, respectively, in the 30% exsanguination group, which were significantly higher than those in the control group (Table 1).

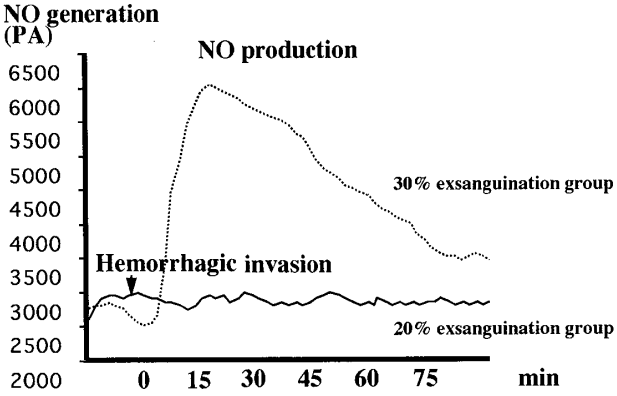

Fig. 1 Change of NO in renal tissue
PA: picoampere.

Renal tissue NO production increased only slightly in the 20% exsanguination group, but quickly increased after hemorrhagic invasion to reach a peak 20 minutes later. Then it tended to gradually become lower in the 30% exsanguination group (Fig. 1).

2. Clinical results

1) Comparison between the deceased and surviving groups (Table 2)

Table 2 Difference in serum iCa^{2+} and clinical feature between deceased and surviving groups with trauma

	Deceased group (n=17)	Surviving group (n=239)
iCa^{2+} (mmol/L)	0.64 ~ 1.16 (0.921±0.183) *	0.58 ~ 1.28 (1.147±0.155)
ISS	26 ~ 66 (mean: 42) * *	1 ~ 59 (mean: 12)
Time from being injured to arrival		
Less than 1 hour	13	209
Less than 4 hours	4	29
More than 4 hours		1
Number of patients with shock on arrival (Systolic blood pressure <80)	15 (88.2%) * *	13 (5.4%)
Base excess (mmol/L)	−30 ~ +2 (−13.62±2.20) * *	−20 ~ +7 (−0.35±0.19)

*p<0.05, * * p<0.01.

The serum iCa^{2+} on arrival at the hospital was 0.64 to 1.16 (mean: 0.921 ± 0.183) mmol/L in the deceased group and 0.58 to 1.28 (mean: 1.147 ± 0.155) mmol/L in the surviving group, with a significant difference between the groups. ISS was 26 to 66 (mean: 42) and 1 to 59 (mean: 12), respectively, indicating a significantly higher score in the deceased group. The time from being injured to arrival at the hospital was less than 4 hours for all the patients but one, with no significant difference between the deceased and surviving groups. The rate of patients with shock on arrival was 88.2% (15/17) in the deceased group and 5.4 % (13/239) in the surviving group, indicating a significantly higher rate in the former group. BE was −30 to +2 (mean: 13.62 ± 2.20) mmol/L in the deceased group and −20 to +7 (mean: − 0.35 ± 0.19) mmol/L in the surviving group, indicating that BE was significantly lower in the former group.

2) Comparison of low and normal serum iCa^{2+} groups in surviving patients (Table 3)

The same parameters were compared between the low and normal serum iCa^{2+} groups of the surviving patients. ISS was 10 to 50 (mean: 29) in the low serum iCa^{2+} group and 1 to 34 (mean: 9) in the normal iCa^{2+} group, indicating that ISS was significantly higher in the former group. The rate of patients with shock on arrival was 37.9% (11/29) and 1.0% (2/210), respectively, indicating a significantly higher rate in the former group. BE was −20 to +6 (mean: − 4.38 ± 0.98) mmol/L and − 5 to + 7 mmol/L (0.25 ± 0.13), respectively, indicating that it was significantly lower in the former group.

3) Change of serum iCa^{2+} during hospitalization

The change of iCa^{2+} during the hospitalization period in 13 evaluable patients is shown in Fig. 2. The serum iCa^{2+} value was low on arrival or fell below the normal range during the hospitalization period without recovery in 3 patients who died in the hospital. In contrast, the remaining surviving patients showed that the value was normal immediately after they were injured or

Table 3 Comparison of patients with low and normal iCa^{2+} in the surviving patients with trauma (n=239)

	Patients with	
	low iCa^{2+} (<1.12 mmol/L) (n=29)	normal iCa^{2+} (1.12 ~ 1.30 mmol/L) (n=210)
Sex Male	23	150
Female	6	60
Age (years)	12~59 (mean: 29)	10~91 (mean: 53)
iCa^{2+} (mmol/L)	0.58~1.11 (0.966±0.040)**	1.12~1.31 (1.156±0.002)
ISS	10~50 (mean: 29)**	1~34 (mean: 9)
Number of patients with shock on arrival (Systolic blood pressure <80)	11 (37.9%)**	2 (1.0%)
Base excess (mmol/L)	−20~+6 (−4.38±0.98)**	−5~+7 (0.25±0.13)

**p<0.01.

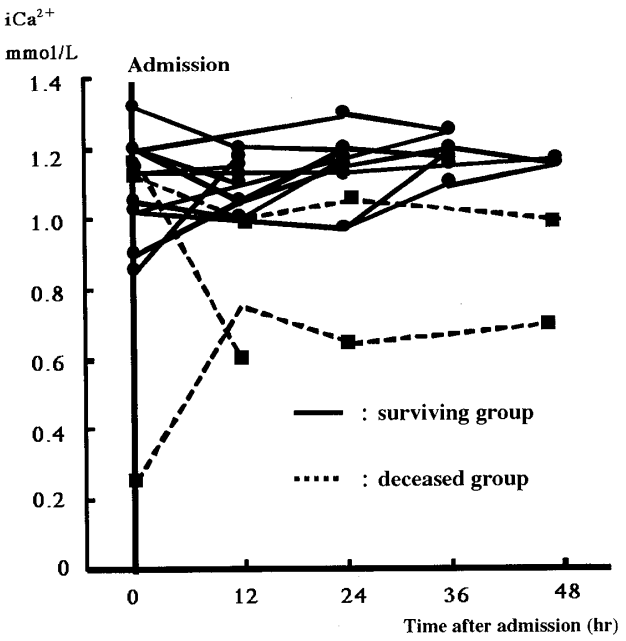

Fig. 2 Change in ionized calcium in patients with serious trauma

returned to normal during the hospitalization period.

Discussion

There are 3 types of calcium in blood: protein-bound calcium, complex calcium, and serum iCa^{2+}. Only serum iCa^{2+} has physiological activity[6]. The metabolism and transportation of serum iCa^{2+} in the body are regulated by parathyroid hormone, calcitonin, and activated vitamin D. The factors to reduce serum iCa^{2+} include measurement conditions (blood dilution[7][8], blood collection, and measurement error) and reduced hormone activity[9)~12]. Like vitamin D, however, parathyroid hormone plays a minor role in acute change in serum iCa^{2+}, as shown by its half-life in blood being several hours. Although the blood half-life of calcitonin is ten or more minutes, calcitonin is secreted by the stimulation from increased serum iCa^{2+} and is not considered to reduce normal serum iCa^{2+}. Moreover, serum iCa^{2+} is known to become lower when it forms complexes with anions of citric acid, lactic acid, and bicarbonate to form a complex-type calcium. The serum iCa^{2+} is also reduced through tissue deposition by pancreatitis and rhabdomyolysis. Recent studies have also shown that the reduced serum iCa^{2+}

from the inflow into cells plays an important role in cell damage and apoptosis after tissue ischemia and shock[13)~15)].

Although cells consume sufficient ATP to keep the difference in ion concentration between the inside and outside of cell membranes, tissue ischemia and shock may eliminate the difference due to the following: ① iCa^{2+} flows into cells from the concentration gradient resulting from the disturbed energy-dependent iCa^{2+} exchange mechanism; ② iCa^{2+} flows into cells with the Na^{+}/Ca^{2+} exchange system due to the increased cellular Na^{+} from ischemia; ③ the increased α-receptor density during ischemia promotes the iCa^{2+} overload after reperfusion; and ④ iCa^{2+} flows into cells from the concentration gradient due to advanced cellular membrane disorder[16)17)]. The above ② is considered the most important[18)]. iCa^{2+} that enters mitochondria disturbs ATP production, thereby causing the cell energy shortage to become worse[19)]. The final damage from iCa^{2+} includes oxidation from free radicals, damage to ion pumps, hydrolysis of membrane phospholipids, and destruction of high polymeric substances in cytoplasm, nucleus, and mitochondria[20)21)].

The present SD experimental rat model of heavy bleeding showed significant reduction of serum iCa^{2+} and significant increase in IL-8 and TNF-α in the animals in which 30% of the whole blood was exsanguinated[22)]. This indicates that heavy bleeding, a main morbid state of serious trauma, can reduce serum iCa^{2+}, and that inflammatory cytokines, such as IL-8 and TNF-α, may be involved in reducing serum iCa^{2+} [23)].

Renal tissue NO production quickly increased to reach a peak after hemorrhagic invasion, and then tended to gradually decrease. NOS exists as 2 isoforms[24)]: one is constitutive NOS (cNOS) that constitutively exists in vascular endothelial cells or nervous tissue and has iCa^{2+}dependent activity[25)] and the other is inducible NOS (iNOS) that is induced to macrophages and neutrophils by cytokines and endotoxin and does not depend on iCa^{2+}[3)26)]. In another experiment of ours[27)], renal tissue NO production was not suppressed by S-methylisothiourea (SMT), a NOS inhibitor with high selectivity for iNOS, but was suppressed by N^{G}-monoethyl-L-arginine (L-NMMA), a NOS inhibitor with low selectivity for iNOS and cNOS, in the 30% exsanguination group[28)]. This suggests that the activation of cNOS and reduction of serum iCa^{2+} may be involved in tissue NO production by hemorrhagic invasion. Fibrin thrombi, a histopathological DIC finding, were observed in the renal and pulmonary microvascular vessels in the 30% exsanguination group. This suggests that DIC may be related to the reduced serum iCa^{2+} and NO production[29)~31)].

Our clinical results showed that the patients who died from trauma showed significantly lower serum iCa^{2+} and BE values and significantly higher ISS and shock rates than the surviving patients. Among the surviving patients, those with low serum iCa^{2+} showed significantly higher ISS and shock rates and significantly lower BE than those patients with normal serum iCa^{2+}. Among the patients with low serum iCa^{2+}, those patients whose serum iCa^{2+} returned to normal from treatment recovered. These clinical data demonstrate that the serum iCa^{2+} reduction may be a good indicator for predicting seriousness and prognosis[2)10)16)32)].

These results indicate that the serum iCa^{2+} is a useful hematological indicator for predicting severity, reaction to treatment, and trauma prognosis. There has not been a specific hematological indicator that can be used for predicting severity, reaction to treatment, and trauma prognosis. Only BE and serum lactic acid have been used as hematological factors for unspecific serious diseases. Clinicians should recognize the importance of serum iCa^{2+} in diagnosing and treating serious

trauma because it can be easily determined by blood gas analysis.

Conclusions

1. When 30% of the whole blood was exsanguinated in the SD experimental rat model of heavy bleeding, serum iCa^{2+} lowered significantly, IL-8 and TNF-α increased significantly, and tissue NO increased. This suggests that iCa^{2+} dependent cNOS may be involved in tissue NO production.

2. In patients with trauma, serum iCa^{2+} was lower in serious cases leading to death and those with high ISS, heavy bleeding, shock, metabolic acidosis, and high inflammatory cytokines.

3. Serum iCa^{2+} can be a useful hematological indicator for predicting severity, reaction to treatment, and trauma prognosis.

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重症外傷における血清イオン化カルシウム濃度—臨床的ならびに実験的検討—

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ショックや組織虚血・再灌流時の細胞障害・細胞死の主な原因が，急速な血清中イオン化カルシウム（iCa^{2+}）の細胞内流入であることが最近の研究で明らかになっている．重症外傷患者は，ショックや呼吸不全を伴い組織虚血を合併することから，受傷後の血清中iCa^{2+}の低下が外傷患者の重症度・緊急度や予後を推定するのに有用である可能性がある．また，侵襲のメディエーターであるNO合成酵素（cNOS）は血清中Ca^{2+}の細胞内流入により活性化されることが報告されている．本研究では，ラットを用いた大量出血モデルにおいて，iCa^{2+}，組織内NOおよび炎症性サイトカインであるIL-8, TNF-αを測定し同時に組織病理像を検討することにより，重症外傷の主病態である大量出血が血清中iCa^{2+}，組織内NO, IL-8, TNF-αに影響を与えるか否かを検討した．また，救急搬送された外傷症例において，搬入時および入院後に血清中iCa^{2+}を測定し，injury severity score（ISS），受傷から搬入までの時間，ショック，血液ガス所見，臨床経過，予後等の各指標と，血清中iCa^{2+}との関連を検討することにより，外傷患者における血清中iCa^{2+}の診断，治療上の意義を検討した．その結果，SDラットを用いた大量出血実験モデルにおいて，全血液の30%放血後iCa^{2+}は有意に低下し，IL-8, TNF-αは有意に上昇した．また，組織内NOは経時的に増加傾向を示した．また，外傷患者の血清中iCa^{2+}は死亡に至る重症例，ISS高値，大量出血，ショック，代謝性アシドーシス等により低下した．以上の結果から血清中iCa^{2+}は，外傷の重症度，治療効果，予後を推定する有用な血液学的指標となりうると考えられた．