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Evaluation of postmortem urea nitrogen, creatinine and uric acid levels in pericardial fluid in forensic autopsy

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Abstract

In postmortem biochemistry, there is insufficient data available for the practical analysis of factors in the pericardial fluid. The aim of the present study was to examine postmortem pericardial fluid for urea nitrogen (UN), creatinine (Cr) and uric acid (UA) levels to investigate the pathophysiology of death in forensic autopsy cases (total, $n=409$; within 48 h postmortem), which included blunt, sharp instrument injury, asphyxiation, drowning, fire fatalities, hyperthermia, hypothermia, methamphetamine-related fatalities, other poisoning, delayed death from trauma and natural diseases. There was a significant elevation in the three markers for chronic renal failure, gastrointestinal bleeding, hyperthermia, hypothermia, methamphetamine fatalities and delayed traumatic death, which was comparable with the clinical criteria for their serum levels. These postmortem findings showed azotemia due to renal failure, elevated protein catabolism and rhabdomyolysis. Although the pericardial levels were otherwise similar to the clinical serum reference ranges, only the drowning fatalities showed significantly lower levels for each marker. These observations suggested the stability of UN, Cr and UA in the pericardial fluid within 48 h postmortem and their usefulness for the pathophysiological investigation of death involving azotemia.

Keywords: Forensic pathophysiology; Postmortem biochemistry; Urea nitrogen; Creatinine; Uric acid; Pericardial fluid

1. Introduction

Postmortem biochemistry is one of the most productive ancillary procedures available to forensic pathologists [1–5]. During the biochemical investigation of cadaveric body fluids, agonal and postmortem interference should be taken into consideration. Using a classical procedure to compare the postmortem findings with clinical data, it was suggested that the most useful blood samples are of peripheral origin [1]. However, previous study suggested that the distribution of nitrogenous compounds in the cardiac and peripheral blood may depend on the cause of death [5]. Further investigations are necessary for more detailed pathophysiological analyses of the blood levels for individual cases, possibly using a reference material. In this respect, the vitreous and pericardial fluids may be investigated for alternative materials [6–19]. Although postmortem interference is also inevitable for vitreous fluid, nitrogenous compounds including urea nitrogen (UN), creatinine (Cr) and uric acid (UA) are relatively stable [5]. Pericardial fluid can also be easily collected without significant contamination. However, there is insufficient published data regarding the practical analysis of these nitrogenous compounds in the pericardial fluid.

In the present study, we comprehensively examined postmortem BUN, Cr and UA levels in the pericardial fluid as markers for investigating the pathophysiology of death.

2. Materials and methods

2.1. Materials

The pericardial fluid of 409 forensic autopsy cases within 48 h postmortem at our institute were examined. The cases

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included 304 males and 105 females, 2 months to 94 years in age (mean of 58.8 years of age) with postmortem intervals between 5 and 47 h. Samples were aseptically collected using syringes and stored at −20 °C, and were centrifuged before assay.

The causes of death were classified as follows: acute traumatic death from blunt injury ($n=65$), sharp instrument injury ($n=15$), mechanical asphyxiation ($n=36$: hanging, $n=6$; strangulation, $n=11$; aspiration, $n=13$; others, $n=6$), drownings ($n=31$: freshwater, $n=15$; saltwater, $n=16$), fire fatalities ($n=80$) consisting of those with blood carboxyhemoglobin (COHb) below 60% ($n=47$) and above 60% ($n=33$), hyperthermia ($n=7$), hypothermia (cold exposure, $n=6$), methamphetamine (MA)-related fatalities (fatal intoxication, $n=7$; other causes of abuser deaths, $n=8$), other poisoning ($n=17$), delayed death from traumas (multiple organ insufficiency, $n=45$; survival time, 3–90 days), acute myocardial infarction/ischemia (AMI, $n=70$), spontaneous cerebral hemorrhages (CH, $n=10$), gastrointestinal (GI) bleeding ($n=5$) and chronic renal failure (uremia, $n=7$) (details shown in Table 1). The above-mentioned causes of death were classified on pathological and toxicological bases. The AMI group consisted of cases of sudden death, which showed macro- and microscopical findings of acute ischemic heart diseases without any evidence of the cause of death being other than due to a cardiac attack [20].

2.2. Biochemical analyses

UN was measured by a urease–glutamate dehydrogenase method [21], Cr by an alkali–picric acid method (modified Jaffe method) [22], and UA by a uricase peroxidase method using an L-type UA Kit (Wako, Tokyo) [23]. Hemoglobin contamination (<0.5 g/dl) did not interfere with the measurements. The clinical reference serum ranges were: 6–20 mg/dl for UN, 0.61–1.04 mg/dl (adult male) and 0.47–0.79 mg/dl (adult female) for Cr, and 3.7–7.6 mg/dl (male) and 2.5–5.4 mg/dl (female) for UA.

2.3. Toxicological analyses

The blood COHb concentrations were determined using a CO-oximeter system [24,25] for all fire fatalities. Volatile chemicals including alcohol were analyzed using head-space gas chromatography for all cases, and drug analyses were performed by gas chromatography/mass spectrometry when preliminary screening tests were positive.

2.4. Statistical analyses

Regression equation analysis was used to compare two parameters including biochemical markers, the age of the victims, the survival time and the postmortem interval. Comparisons between groups were performed using the

Table 1
Case profiles ($n=409$)

Cause of death	n	Male/Female	Age (years)		Survival time (h)		PMI (h)	
			Range	Median	Range	Median	Range	Median
Blunt injury	65	53/12	10–94	55.0	<0.5–24	1.5	9–44	19.8
Sharp instrument injury	15	11/4	38–90	60.0	<0.5–16	<0.5	7–42	16.9
Asphyxia	36	22/14	0–93	55.0	<0.5		6–44	18.3
Drowning								
Freshwater	15	10/5	45–79	60.0	<0.5		9–36	20.0
Saltwater	16	11/5	0–73	47.0	<0.5		7–47	18.7
Fire fatality								
COHb <60%	47	39/8	23–93	66.0	<0.5		6–36	16.3
COHb >60%	33	23/10	1–87	68.0	<0.5		5–42	12.3
Hyperthermia	7	5/2	15–88	72.0	3–14	5.0	9–31	20.5
Hypothermia	6	5/1	44–76	57.0	3–6	3.0	6–44	16.3
MA-related fatalities								
MA poisoning	7	6/1	20–52	38.0	3–24	4.5	22–45	29.0
other MA-abuser fatalities	8[a]	6/2	20–59	45.0	<0.5–22	<0.5	10–24	13.8
Other poisoning	17[b]	12/5	20–87	56.0	<0.5–24	5.0	13–42	25.0
Delayed traumatic death	45[c]	33/12	1–83	59.0	72–2,160	59.0	5–30	13.1
Natural diseases								
Acute myocardial infarction/ischemia	70	53/17	43–94	67.0	<0.5–11	<0.5	6–42	19.7
Spontaneous cerebral hemorrhages	10	5/5	45–81	64.0	0.5–19	1.5	5–39	22.4
Chronic renal failure	7	5/2	46–89	78.0	unknown		9–27	17.3
Gastrointestinal bleeding	5	5/0	50–67	61.0	1–8	2.0	10–31	14.6

PMI, postmortem interval; COHb, carboxyhemoglobin concentration; MA, methamphetamine.

[a] Asphyxia ($n=3$), death due to injury ($n=2$), burns ($n=1$), acute myocardial infarction ($n=1$) and spontaneous cerebral hemorrhage ($n=1$).

[b] Sedative–hypnotics ($n=4$), sodium cyanide ($n=2$), ethanol ($n=3$), carbon monoxide ($n=3$) and others ($n=4$).

[c] Multiple organ insufficiency and secondary infection from head injury ($n=39$) and chest injury ($n=6$).

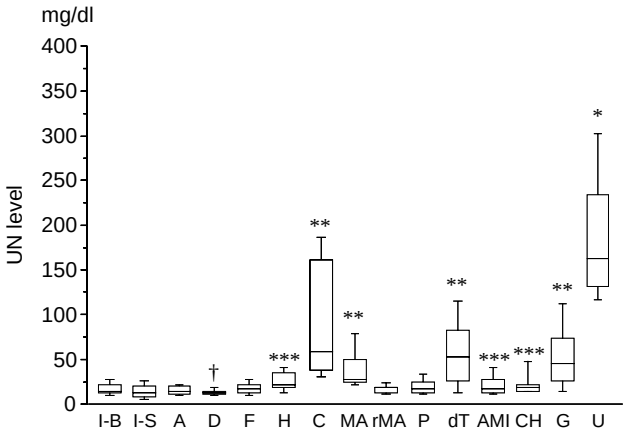

Fig. 1. Pericardial urea nitrogen (UN) levels in relation to the cause of death. I-B, blunt injury; I-S, sharp instrument injury; A, asphyxiation; D, drownings; F, fire fatalities; H, hyperthermia; C, hypothermia; MA, fatal methamphetamine intoxication; rMA, other MA abuser fatalities; P, other poisoning; dT, delayed traumatic death; AMI, acute myocardial infarction/ischemia; CH, spontaneous cerebral hemorrhages; G, gastrointestinal bleeding; U, chronic renal failure (details shown in Table 1). Significantly high: *U vs. other groups ($P<0.001$); **C, dT and G vs. I-B, I-S, A, D, F, rMA, P, AMI and CH ($P<0.001$); MA vs. I-B, I-S, A, D, F ($P<0.001$), rMA, P ($P<0.01$), AMI and CH ($P<0.05$); ***H, AMI and CH vs. A ($P<0.01$), I-B and I-S ($P<0.05$). Significantly low: †D vs. I-B, F ($P<0.01$), rMA and P ($P<0.05$).

Mann–Whitney U test. These analyses were performed using Microsoft Excel and Statview (version 5.0, SAS Institute Inc.), and a P-value less than 0.05 was considered significance. In Figs. 1–4, the results of the data analysis are shown as box-plots, for which 50% of the data are summarized in the box. The line in each box represents the median and the lines outside of each box represent the 90% confidence interval.

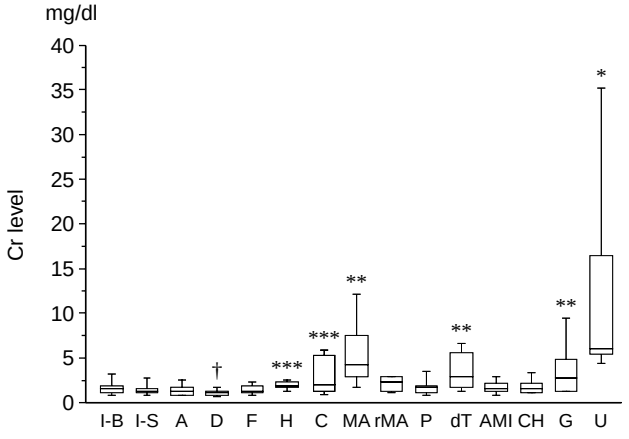

Fig. 2. Pericardial creatinine (Cr) levels in relation to the cause of death for subjects over 18 years of age. The abbreviations used are shown in Fig. 1. Significantly high: *U vs. other groups ($P<0.001$); **dT, MA vs. I-B, I-S, A, D, F and AMI ($P<0.001$); G vs. D ($P<0.01$), A and F (<0.05); ***H vs. A ($P<0.01$), I-B, I-S and F ($P<0.05$); C vs. A ($P<0.01$) and F ($P<0.05$). In addition, dT vs. CH ($P<0.01$), MA vs. rMA and CH ($P<0.01$). Significantly low: †D vs. AMI ($P<0.001$), I-B, F, rMA, P ($P<0.01$), I-S and CH ($P<0.05$). The gender difference (males > females) was significant for I-B, D and AMI ($P<0.05$).

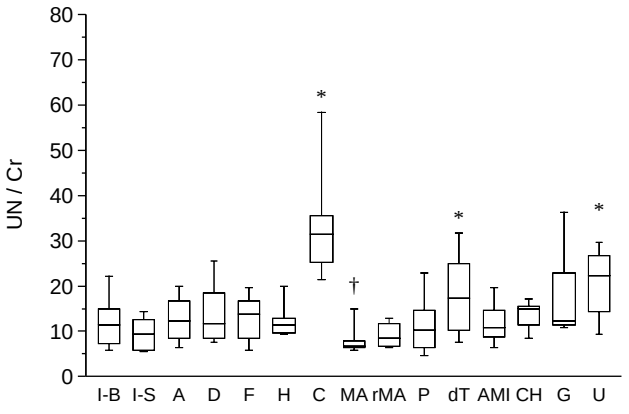

Fig. 3. Pericardial urea nitrogen/creatinine (UN/Cr) ratio in relation to the cause of death for subjects over 18 years of age. The abbreviations used are shown in Fig. 1. Significantly high: *C, U and dT vs. I-B, I-S, A, D, F, H, MA, rMA, P, AMI, G ($P<0.001$) and CH ($P<0.05$). Significantly low: †MA vs. A, F ($P<0.01$) and CH ($P<0.05$).

3. Results

3.1. Postmortem stability, age- and gender-dependence

The postmortem ranges for the pericardial fluid were: UN, 16–313 mg/dl (mean/median, 27.2/17.2); Cr, 0.33–39.54 mg/dl (mean/median, 2.18/1.46); UA, 0.8–35.2 mg/dl (mean/median, 6.2/5.3). For all cases, each factor did not show any significant relationship with the postmortem intervals (correlation coefficient, $r<0.1$; $P>0.1$), and there was a tendency to increase depending on the survival time within 7 days ($n=385$, $r>0.3$, $P<0.001$). For subjects below 18 years of age (x in age), an age-dependent increase was observed for the Cr level (y): $y=0.066x+0.806$, $n=20$, $r=0.43$, $P<0.05$). For adult subjects over 18 years of age,

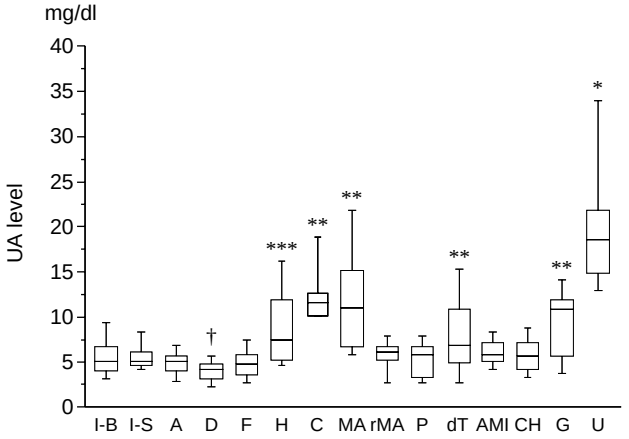

Fig. 4. Pericardial uric acid (UA) levels in relation to the cause of death. The abbreviations used are shown in Fig. 1. Significantly high: *U vs. other groups ($P<0.001$); **H, C and MA vs. I-B, I-S, A, D, F, P and AMI ($P<0.001$); dT and G vs. D ($P<0.01$), I-B, I-S, A, F and AMI ($P<0.05$); ***H vs. D, F ($P<0.01$), I-B and A ($P<0.05$). In addition, MA vs. rMA and CH ($P<0.05$). Significantly low: †D vs. AMI ($P<0.001$), I-B, I-S, rMA ($P<0.01$), A, F, P and CH ($P<0.05$). The gender difference (males > females) was significant for AMI ($P<0.05$).

the Cr and UA levels were significantly higher for males (mean/median: Cr, 2.40/1.60 mg/dl; UA, 6.61/5.55 mg/dl) than for females (mean/median: Cr, 1.55/1.17 mg/dl; UA, 4.89/4.75 mg/dl) ($P<0.01$).

3.2. Differences in relation to the causes of death

3.2.1. Urea nitrogen

The UN level was usually low (median, <20 mg/dl) for the blunt injury, sharp instrument injury, asphyxiation, drowning and fire fatalities, for which 78.3% of the cases ($n=162/207$) were included within the clinical reference range (6–20 mg/dl). In comparison, there was a marked elevation for the cases of chronic renal failure, and a moderate elevation for the fatal hypothermia, GI bleeding, MA fatalities and delayed traumatic death. However, for the other MA abuser fatalities, UN level (10.9–25.3 mg/dl, median, 17.4) was not elevated, showing a significant difference from fatal MA intoxication ($P<0.01$). There was a mild increase in the cases of hyperthermia, AMI and CH compared with cases of blunt injury, sharp instrument injury and asphyxiation. The cases of drowning showed a slightly lower level (Fig. 1). When cases showing higher levels (chronic renal failure, MA fatalities, delayed traumatic deaths, GI bleeding, hyperthermia and hypothermia) and lower levels (drowning) were excluded, the postmortem pericardial UN level was 18.4 ± 9.6 mg/dl (mean$\pm$SD) with a median of 16.0 mg/dl ($n=301$) without any gender difference.

3.2.2. Creatinine

For adult subjects over 18 years of age, the Cr level was relatively low (median, <1.5 mg/dl) for the blunt injury, sharp instrument injury, asphyxiation, drowning and fire fatalities. When compared with these groups, there was a marked elevation in chronic renal failure and a moderate elevation for the MA fatalities, delayed traumatic deaths and GI bleeding, which was more evident for males. The MA fatalities showed a higher level compared with other MA abuser fatalities ($P<0.01$), which showed a mild increase for males. The cases of hyperthermia and hypothermia also showed a mild to moderate elevation (Fig. 2). The UN/Cr ratio was relatively high for chronic renal failure (7.9–29.5; median, 22.3), hypothermia (20.8–60.7; median, 31.0) and delayed traumatic death (6.5–46.9; median, 19.4), whereas it was low for hyperthermia (8.0–20.9; median, 10.1), MA fatalities (5.6–15.7; median, 6.7) and GI bleeding (10.8–36.4; median, 12.0), all showing a significant difference (Fig. 3). In addition, there was a slightly lower Cr level for the drowning fatalities. There was no significant difference between the fresh- and saltwater drownings or between the subgroups of fire fatalities with a lower and higher COHb.

When cases showing higher levels (chronic renal failure, MA fatalities, delayed traumatic deaths, GI bleeding, hyperthermia and hypothermia) and lower levels (drowning) were excluded, the postmortem pericardial Cr level was 1.89 ± 1.28 mg/dl (mean$\pm$SD) with a median of 1.52 mg/dl ($n=215$) for adult males and 1.41 ± 0.80 mg/dl (mean$\pm$SD) with a median of 1.14 mg/dl ($n=71$) for adult females, showing a significant gender difference (males > females, $P<0.001$).

3.2.3. Uric acid

The UA level was usually low (median, <7.0 mg/dl) for the blunt injury, sharp instrument injury, asphyxiation, drowning and fire fatalities. When compared with these groups, there were marked elevations for the chronic renal failure and a moderate elevation for hyperthermia, hypothermia, MA fatalities, delayed traumatic death and GI bleeding. The MA fatalities showed a higher level compared with other MA abuser fatalities for males ($P<0.05$). The cases of drowning showed a slightly lower level (Fig. 4). Differences between the fresh- and saltwater drownings or between the subgroups of fire fatalities were insignificant.

When cases showing higher levels (chronic renal failure, MA fatalities, delayed traumatic deaths, GI bleeding, hyperthermia and hypothermia) and lower levels (drowning) were excluded, the postmortem pericardial UA level was 5.96 ± 2.70 mg/dl (mean$\pm$SD) with a median of 5.40 mg/dl ($n=224$) for males and 4.84 ± 1.68 mg/dl (mean$\pm$SD) with a median of 4.90 mg/dl ($n=77$) for females, showing a significant gender difference (males > females, $P<0.01$).

4. Discussion

The usefulness of pericardial fluid for postmortem toxicological and biochemical investigation has been suggested [6–19,26]. The present study showed no significant influence of early postmortem changes within 48 h after death on UN, Cr and UA in the pericardial fluid as was observed for their serum levels [5]. The Cr and UA levels were significantly higher in males, and Cr showed age dependence. These findings are comparable with previous clinical data (reference intervals: Cr, 0.61–1.04 for adult males and 0.47–0.79 for adult females; UA, 3.7–7.6 for adult males and 2.5–5.4 for adult females) and can be attributed to differences in the amounts of skeletal muscles present in individual subjects [27]. When this age- and gender-dependent factor was taken into consideration, a significant concomitant elevation in the pericardial UN, Cr and UA levels with a relatively high UN/Cr ratio (>10) was observed for the cases of uremia, hypothermia (cold exposure) and delayed traumatic death. The clinical reference value for the UN/Cr ratio is approximately 10:1. Values markedly greater than this suggest that the cause of an elevated UN is prerenal than renal, whereas lower values suggest an increase in creatine turnover [27–29]. In the present study, similar findings were observed in autopsy cases, thus suggesting that these criteria may also be

available for postmortem investigation. In addition, azotemia was noted in the GI bleeding cases. These postmortem findings in the pericardial UN, Cr and UA levels for renal failure and elevated protein catabolism are comparable to the clinical criteria for their respective serum levels [27–29].

MA fatalities showed a marked elevation in their pericardial Cr and UA levels with a relatively low UN/Cr ratio (<10) accompanied by a moderate UN elevation. This is comparable with the clinical biochemical features of MA toxicity including increases of serum Cr and UA, which may be related to advanced skeletal muscle damage (rhabdomyolysis) [27,30–32]. Similar findings were observed for hyperthermia. Although such findings were not evident for the MA abusers who died from other causes, a mild elevation in Cr was observed, suggesting rhabdomyolysis. This finding may be important when analyzing the influence of MA abuse in such cases, where MA may have led to traumatic death because of the abnormal behavior or death from an attack of cardiac or cerebrovascular disease due to the circulatory influence involving hypertension [33–37].

For the other acute traumatic causes of death including blunt and sharp instrument injuries, asphyxiation, drowning and fire fatalities, the pericardial levels of the three markers approximated their clinical serum reference ranges, although there was a mild elevation especially in the Cr level. For the AMI and CH cases, which were usually associated with systemic atherosclerosis, the pericardial UN level was mildly elevated, suggesting the pre-existence of reduced renal function [27].

The pericardial fluid is a transudate derived from the epicardium and contains plasma components and also various substances derived from myocardial interstitial tissues [38–40]. The turnover rate of albumin in the pericardial effusion is estimated to be days using its half-life time [40]. This suggests that, although the turnover of smaller substances such as electrolytes, minerals and nitrogenous compounds may be more rapid, a considerable delay may occur in terms of changes in such components of the pericardial fluid during systemic metabolic deterioration. The above-mentioned elevation in pericardial UN, Cr and UA levels for hyperthermia, hypothermia, delayed traumatic death, MA fatalities, chronic renal failure and GI bleeding is suggestive of persistent metabolic deterioration before death. With respect to this, the pericardial fluid may be useful for analyzing pre-existing diseases associated with azotemia in acute death cases.

Although a previous study showed that the elevation in serum Cr and UA levels for acute deaths is accompanied by massive skeletal muscle damage and advanced hypoxia such as for asphyxiation and fire fatalities [5], their pericardial levels were found to be relatively low in the present study. This can be attributed to the nature of the pericardial fluid, in which the turnover rates are much milder than those in the blood. A comparison between the blood and pericardial levels may be useful when investigating acute metabolic changes in nitrogenous compounds. However, only the cases of drowning showed significantly lower levels of UN, Cr and UA in comparison with the other groups, and this may be related to water aspiration [41–43]. With respect to these findings, further investigations are necessary.

In conclusion, this comprehensive study first provided the reference data of UN, Cr and A levels in cadaveric pericardial fluid, suggesting their substantial postmortem stability. These markers may be useful for determining the delayed cause of traumatic death and MA fatalities and also assessing pre-existing diseases associated with azotemia for cases of acute death, and may be comparable with clinical criteria for their respective serum levels. In addition, it may also be helpful for making the diagnosis of drowning. Furthermore, a comparison between the blood and pericardial levels may be useful when investigating acute changes of serum nitrogenous compounds.

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