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Cameron S. Crandall,[1] *M.D.; Sarah Kerrigan,*[2] *Ph.D.; Roberto L. Agüero Blau,*[1] *M.Sc.; Jonathon LaValley,*[1] *B.S.; Ross Zumwalt,*[3] *M.D.; and Patrick E. McKinney,*[1,*] *M.D.*

The Influence of Site of Collection on Postmortem Morphine Concentrations in Heroin Overdose Victims

ABSTRACT: When assaying for postmortem morphine concentration, significant site sampling variability exists between central and peripheral sampling sites and even within sampling regions of the body. To study the variation, 76 suspected heroin overdoses were identified. Each had femoral artery (FA) and vein (FV), left and right ventricle and pooled heart blood samples obtained at autopsy. Forty-four tested positive for morphine. Morphine concentrations were determined by gas chromatography/mass spectrometry, with sampling site differences reported as log-transformed ratios and compared by signed rank test.The mean FA to FV ratio for total morphine was 1.2 (range 0–4.5). The ratio for left heart to right heart total morphine was 1.1 (range 0.4–3.2). Left ventricular to FV total morphine ratio was 2.0 (range 0.6–6.9). In these opioid overdose deaths, FA and FV morphine concentrations are usually similar, although up to 4.5-fold differences were noted. Centrally obtained morphine concentrations are on average twice as high compared with peripheral morphine concentrations. Left and right ventricular morphine concentrations were usually similar, although up to 3.2-fold differences were noted (left side higher).

KEYWORDS: forensic science, postmortem, blood, morphine, heroin, fatality, overdose

Drug, especially opioid-related, fatalities increased dramatically throughout the United States, Great Britain, and Australia during the 1990s, reflecting increased use of heroin throughout the world during that period (1–3). This increase was also true in New Mexico where the state medical examiner (the Office of the Medical Investigator (OMI)) reported between 100 and 140 opiate deaths per year and demonstrated a substantial mortality rate increase over that decade (4).

In addition to the illicit use of opioids, drugs of this class are frequently prescribed to treat acute and chronic pain. Combinations of narcotics and analgesics are the most frequently mentioned central nervous system agents in medication-related emergency department visits (5). Additionally, both short- and long-acting opioids are commonly prescribed for painful conditions, especially when associated with chronic diseases with chronic pain, such as cancer (5). Consequently, postmortem toxicology testing often reveals the presence of a variety of opioids in a large number of autopsy cases. Despite this frequency, interpretation of postmortem blood morphine concentrations is complicated by many factors that include overlapping therapeutic, toxic, and fatal concentrations.

Despite the upward trend of opioid-related fatalities, the complexity of forensic pathology and the unique aspects of each case proscribe the development of a national standard for specimen collection. In addition, particular aspects of specimen collection (e.g., site and volume) influence the outcome of blood morphine concentrations and subsequently the relationship to antemortem values. Typically heart or femoral blood samples are used for postmortem drug testing. However, the majority of scientific papers describing postmortem blood morphine concentrations omit the details of specimen collection, and this information may be critical in interpreting the data and applying it to the individual forensic case (6–7). Femoral specimens taken in the field involve a blind needle aspiration in the inguinal region that may yield either venous or arterial blood or both. Concentrations of many drugs are known to differ significantly in patients between arterial and venous specimens, likely as a result of metabolism or repartitioning (8). It is reasonable to posit that these differences persist in death. However, postmortem data regarding arterial vs. venous drug concentrations from paired arteries and veins are limited, and data regarding opioid concentrations are limited, to individual cases (9–10). For example, Jones and Pounder (9) described a suicide involving multiple drugs including codeine where codeine concentrations in the inferior vena cava and abdominal aorta were similar. Unfortunately, there has been no systematic comparison of femoral arterial and venous drug concentrations in forensic cases.

At autopsy, a pathologist may sample blood from the heart when a femoral specimen is not available or as a means of corroborating the femoral specimen. Specimen collection usually occurs by incising the heart at the posterior aspect where the inferior vena cava inserts to the right atrium. The pathologist aspirates this resulting pool of blood from the thoracic cavity. These specimens are collectively termed "heart blood" although it is a composite of atrial and caval blood. Investigators often omit details of specimen collection such as volume of collection and specific chamber of the heart. There are no systematic postmortem comparisons

[1] Department of Emergency Medicine, Center for Injury Prevention Research and Education, University of New Mexico, Albuquerque, NM. 87131-0001.
[2] College of Criminal Justice, Sam Houston State University, Huntsville, TX 77341.
[3] New Mexico Office of the Medical Investigator, Albuquerque, NM. 87131-0001.
*Deceased.

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of drug concentrations in left vs. right heart blood among suspected morphine overdose fatalities. However, Moriya and Hashimoto (10) demonstrated that morphine concentrations detected from left heart blood are almost twice as high as concentrations detected from right heart blood (both free and total) from the same individual.

Site dependence is a question explored in studies of morphine concentrations. In two studies examining the postmortem redistribution of morphine in rats, morphine concentrations in heart blood rose with time after death (6–7). However, authors did not report details regarding sample collection including specific chamber of the heart, type of blood vessel, and sample size. A third, and contradictory, study in rabbits using similar methods found that heart-blood morphine concentrations decreased with time after death (11). Direct comparison of the data is complicated, however, by the absence of a nationally standard protocol and the lack of detail describing how samples are collected.

Hypothesis

The hypothesis of this study was that postmortem morphine concentrations differed according to site: venous vs. arterial vessel at the femoral site and left vs. right heart. Data obtained from this study may elucidate the conflicting results observed in the literature and facilitate recommendations for standardized collection of postmortem specimens used to determine toxicologic cause of death in cases of morphine (heroin) exposure.

Methods

Study Period and Inclusion Criteria

In New Mexico, poisoning deaths fall under the jurisdiction of the Office of the Medical Investigator unless occurring on Federal lands such as military bases and Indian reservations. Autopsies are performed in almost all poisoning fatalities and toxicological analyses of blood specimens for morphine and/or metabolites are conducted. Seventy-six suspected heroin related deaths were enrolled in the study during the period 1 September 2002 through 7 April 2003. Table 1 lists demographic and autopsy characteristics. Of these 76 cases, 44 (58%) tested positive for morphine and morphine metabolites and were therefore included in the study; the remainder had no detectable morphine and tested positive for drugs other than morphine (e.g., cocaine ($n = 28$)).

TABLE 1—*Sample characteristics of suspected heroin overdoses of identifiable remains.*

	Suspected Heroin Overdose Decedent		Morphine Present in Toxicologic Analyses		Morphine Not Present in Toxicologic Analyses	
	$n = 76$		$n = 44$		$n = 32$	
	N	%	*N*	%	*N*	%
Demographics						
Sex						
Male	60	84.5	38	88.4	22	78.6
Female	11	15.5	5	11.6	6	21.4
Unknown	5		1		4	
Race						
Hispanic	45	64.3	31	72.0	15	53.6
White/Anglo	21	30.0	10	23.3	11	39.3
American Indian	4	5.7	2	4.7	2	7.1
Unknown	6		1		5	
Age group (years)						
18–32	19	26.8	9	20.9	10	35.7
33–49	40	56.3	26	60.5	14	50.0
50 and older	12	16.9	8	18.6	4	14.3
Unknown	5		1		4	
Autopsy characteristics						
Fresh track marks						
Yes	46	66.7	33	76.7	14	51.9
No	23	33.3	10	23.3	13	48.1
Unknown	7		1		6	
Syringe found at scene						
Yes	30	46.9	19	51.4	11	39.3
No	34	53.1	18	48.6	17	60.7
Unknown	12		7		5	
Drugs found at scene						
Yes	10	17.6	9	27.2	1	4.0
No	47	82.5	24	72.8	24	96.0
Unknown	19		11		8	
Decomposition						
Yes	12	17.7	5	11.9	7	25.9
No	56	82.4	37	88.1	20	74.1
Unknown	8		2		6	
Time to sampling (hours)						
1–24	38	52.8	23	52.3	15	53.6
25–48	25	34.7	17	38.6	8	28.6
49+	9	12.5	4	9.1	5	17.8
Unknown	4		2		2	

Sample Collection

Data collected from these cases included time of death, morphine concentrations from blood samples at 5 sites, as well as any descriptive data about the decedent at time of death. In each case, the examiner visualized the iliac vessels (femoral artery (FA), femoral vein (FV)) from the abdominopelvic cavity. A long catheter was inserted into each vessel and directed caudally and blood samples were aspirated. The iliac vessels were digitally occluded proximal to the catheter insertion site to prevent aspiration of central blood. For the purposes of this study, a 3 mL sample was aspirated from each vessel. Heart blood samples were taken (3 mL volume) directly from the left and right ventricles (LV and RV) and processed the same as femoral blood specimens. When insufficient blood was available by aspiration from the left ventricle, it was incised and the entire contents were collected, avoiding contamination with extra-cardiac blood/fluid. The LV, followed by RV specimens, were each successively aspirated with a clean 20 mL syringe. At some autopsies, additional heart blood was also collected by incising the pericardium at the posterior surface of the heart, near the insertion of the inferior vena cava to the right atrium (POOL). This method allowed a large amount of blood to POOL in the pericardium/thoracic cavity. Five samples were therefore obtained from each patient (where available). All whole-blood specimens were stored at 4°C in gray-top tubes containing sodium fluoride (preservative) and potassium oxalate (anticoagulant).

Quantitative Analysis

A small aliquot of cardiac blood was collected. All heart samples from each individual patient were then pooled and mixed for additional testing. Morphine and its glucuronide conjugates were measured by Gas Chromatography/Mass Spectroscopy (GC/MS).

Morphine was isolated from whole blood using a polymeric Cerex Clin II solid phase extraction (SPE) cartridge (SPEware, SPEware Corporation, San Pedro, CA). Silanized glassware was

used throughout. Deuterated internal standard (morphine-d3, Cerilliant, Cerilliant Corporation, Round Rock, TX) was added to 1 mL of sample to give a final concentration of 0.25 mg/L. Proteins were precipitated by addition of cold acetonitrile (2 mL), while vortex mixing followed by centrifugation for 10 min at 4000 rpm. The supernatant was transferred to a clean glass tube and 1 mL of 0.1 M HCl was added. Acidified samples were added to SPE columns and allowed to flow under gravity. Columns were then washed successively with 1 mL aliquots of deionized water, 0.1 M HCl, methanol, ethyl acetate, and dried under vacuum for 5 min. Morphine was eluted from the column using 1 mL methylene chloride/isopropyl alcohol (80:20) containing 2% concentrated ammonium hydroxide. Extracts were evaporated to dryness under nitrogen. Samples were reconstituted using 15 μL ethyl acetate and 15 μL N-methyl-N-trimethylsilyltrifluoroacetamide (MSTFA) followed by derivatization at 70°C for 15 min in a tightly sealed glass tube. Derivatized extracts were then cooled to room temperature and injected onto the GC/MS.

For total morphine determination, deuterated morphine-3-glucuronide was used as the internal standard. Following addition of 0.25 mg/L morphine-3-glucuronide-d3 (Cerilliant), samples were incubated for 3 h at 37°C with 5000 Units of *Escherichia coli* Type IX β-glucuronidase (Sigma, Sigma Chemical Company, St. Louis, MO). After deconjugation and cooling to room temperature, samples were assayed for morphine as described above.

An Agilent HP 5973 MSD (Agilent Technologies, Palo Alto, CA) with 30m DB-5 column (0.25 mm i.d. × 25 μm film thickness) was used for separation and identification. A 2 μL splitless injection was delivered onto the column, which was temperature-programmed as follows: initial temperature 160°C with a ramp of 30°C/min to 260°C (hold 2 min), then 30°C/min to 290°C (hold 5 min). The injector and interface temperatures were 250°C and 280°C, respectively. Data were acquired by selective ion monitoring (*m/z* 429, 324, 287 for morphine and 432, 327, and 291 for morphine-d3; quantitation ions are shown in bold). Calibration curves were constructed between 0.010 and 1.000 mg/L by fortification of bovine blood with the appropriate drug standard. R^2 values in the linear range were 0.999 or greater. The limits of morphine detection and quantification were 0.005 and 0.010 mg/L. These were defined as the lowest concentration of drug that produced a signal to noise ratio of 3:1 or 10:1, respectively, and with ion ratios with acceptable limits (± 20%). Accuracy was 93–97% using in-house controls fortified with free morphine between 0.015 and 0.950 mg/L, and 89–104% for total morphine in the range 0.067–0.417 mg/L. Replicate analysis of a commercial whole blood control (Utak Laboratories, Utak Laboratories, Inc., Valencia, CA) indicated 104% accuracy and an intraassay CV of 6.6% ($n = 4$). A commercial free morphine whole blood control was included with each run in addition to in-house controls for both free and total morphine.

Statistical Analysis

Data were analyzed using both the raw (untransformed) and natural log-transformed values for both free and total morphine concentrations. The natural log transformation is frequently applied to concentration data as it tends to make the distribution of the values symmetric about the mean as well as stabilizing the variance by amplifying the variance at low values while reducing the variance at high values, i.e., it reduces heteroscedasticity.

As a measure of agreement between sampling sites, we calculated ratios on untransformed values. As a measure of overall relativity, site values for both free and total morphine concentrations were compared within each decedent to the FV site. We calculated additional comparative ratios for (1) LV to the RV as a measure of differences between pre- and postpulmonary metabolism as well as calculating (2) the central to peripheral ratio (*C/P*) ([RV] × [LV]/[FV] × [FA]).

To test for the effect of time to sampling on morphine concentration, log free and log total morphine values were regressed against the number of hours to sampling. The model was coerced to have no intercept. The slope of the regression line approximated the apparent decline in morphine over time.

Inference testing for morphine values was conducted only on the log-transformed data. A generalized linear modeling approach was used to test for differences in the mean values of morphine concentrations between the different sampling sites. Tukey's Honestly Significant Difference (HSD) post-hoc procedure was used to adjust for multiple comparisons.

For all statistical inference, we used a two-tailed Type I error rate of 5%, or we calculated 95% confidence intervals about the point estimate.

Data were entered into a Microsoft Excel spreadsheet, then transferred to SAS (SAS Institute, version 9.0, Cary, NC) for data management and analysis. Graphical analyses were conducted in S-Plus (Insightful Corporation, version 6.2, Seattle, WA).

Results

Of the cases included in this study from the enrollment population ($n = 44$), most were male (88%, $n = 38$) and the majority of were Hispanic (72%, $n = 31$). Of the remainder, 23% were Anglo

TABLE 2—*Summary statistics and comparison ratios for free morphine concentrations (mg/L) at various sampling sites.*

	N	Median	Mean	Lower 95% CI	Upper 95% CI
Free morphine concentration					
Site					
Base values					
FV	44	0.13	0.17	0.12	0.22
FA	41	0.12	0.20	0.13	0.27
LV	42	0.20	0.30	0.20	0.40
RV	42	0.17	0.24	0.17	0.32
Pool	43	0.16	0.23	0.17	0.29
FV ratio					
FA/FV	37	1.17	1.21	1.02	1.41
LV/FV	38	1.65	1.88	1.53	2.23
RV/FV	38	1.42	1.51	1.35	1.54
POOL/FV	39	1.36	1.39	1.24	1.98
Central to peripheral ratio					
(RV × LV)/(FV × FA)	36	2.07	3.63	1.72	5.54
Log-transformed free morphine concentration					
Site					
Base values					
FV	40	−2.03	−1.96	−2.20	−1.71
FA	38	−2.07	−1.96	−2.27	−1.65
LV	40	−1.59	−1.51	−1.78	−1.25
RV	40	−1.74	−1.66	−1.90	−1.42
Pool	41	−1.77	−1.73	−1.99	−1.46
FV ratio					
FA/FV	36	0.92	0.93	0.71	1.06
LV/FV	37	0.76	0.65	0.49	0.81
RV/FV	38	0.86	0.77	0.67	0.87
POOL/FV	38	0.85	0.82	0.76	0.88
Central to peripheral ratio					
(RV × LV)/(FV × FA)	35	0.66	0.65	0.31	0.98

FA, femoral artery; FV, femoral vein; RV, right ventricle; LV, left ventricle; POOL, thoracic pool specimen; CI, confidence interval.

TABLE 3—*Summary statistics and comparison ratios for total morphine concentrations (mg/L) at various sampling sites.*

	N	Median	Mean	Lower 95% CI	Upper 95% CI
Total morphine concentration					
Site					
Base values					
FV	44	0.53	0.85	0.50	1.20
FA	41	0.56	0.86	0.48	1.24
LV	42	0.75	1.18	0.80	1.57
RV	42	0.84	1.32	0.86	1.78
Pool	43	0.72	1.18	0.77	1.59
FV ratio					
FA/FV	41	1.10	1.23	0.99	1.47
LV/FV	42	1.54	1.87	1.47	2.28
RV/FV	42	1.76	2.00	1.55	2.44
POOL/FV	43	0.98	1.02	0.88	1.17
Central to peripheral ratio					
(RV × LV)/(FV × FA)	41	2.82	5.00	2.78	7.22
Log-transformed total morphine concentration					
Site					
Base values					
FV	44	−0.63	−0.59	−0.86	−0.33
FA	41	−0.57	−0.61	−0.91	−0.31
LV	42	−0.28	−0.20	−0.47	0.06
RV	42	−0.17	−0.13	−0.41	0.15
Pool	43	−0.31	−0.26	−0.54	0.03
FV ratio					
FA/FV	40	0.79	1.54	0.13	2.95
LV/FV	41	0.566	−0.02	−1.38	1.32
RV/FV	41	0.76	0.86	−1.10	2.82
POOL/FV	42	0.59	0.90	−0.94	2.75
Central to peripheral ratio					
(RV × LV)/(FV × FA)	39	0.28	0.67	−0.83	3.17

FA, femoral artery; FV, femoral vein; RV, right ventricle; LV, left ventricle; POOL, thoracic pool specimen; CI, confidence interval.

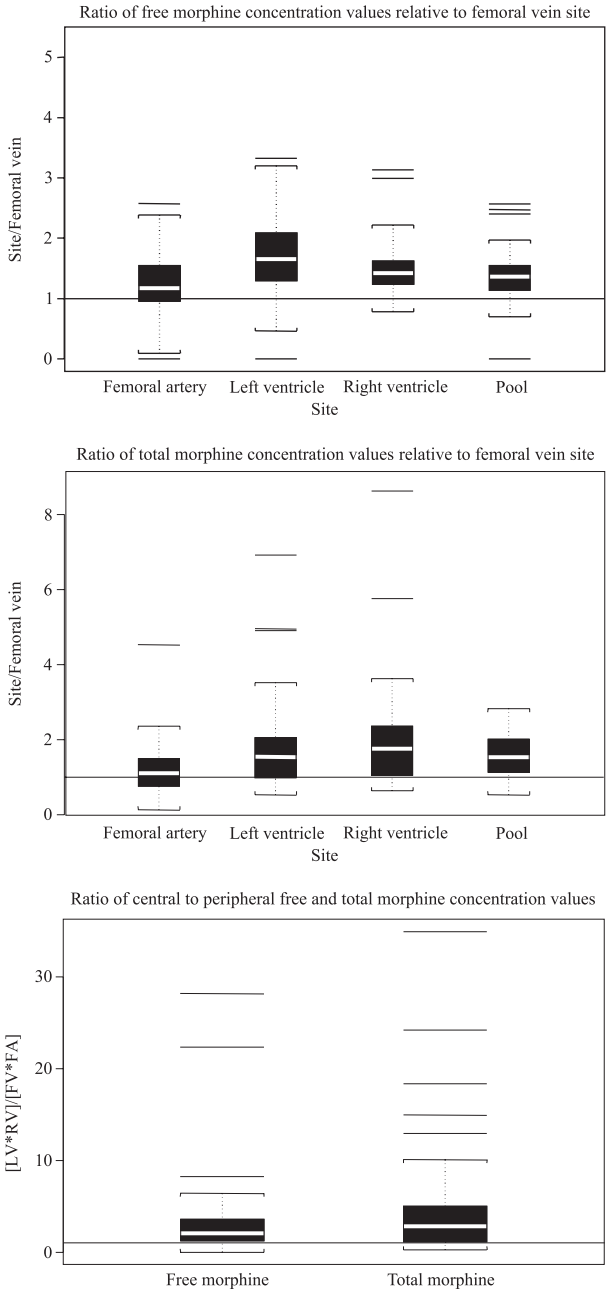

FIG. 1—*Side-by-side boxplots of site morphine concentration values relative to femoral vein site or central to peripheral ratio (C/P).*

and 5% Native American. The average age of the sample population was 40.1 years (SD = 10.6, median = 41.5 years). Males and females had a similar age distribution. Regarding some characteristics associated with the deaths, recent needle puncture marks were observed on 77% ($n = 33$) of the opioid overdose cases. Drug-related paraphernalia found at the location of death included syringes (51%) as well as the drugs of abuse (27%). Postmortem decomposition was noted in 12% ($n = 5$). When available, the mean time between death and sampling of all cases was 27.8 h ($n = 39$, SD = 16.3, and median 24.5 h) with a range of 62.5 h (min = 0 h (patient dead in ED) and max = 62.5 h).

Presence of fresh-injection track marks (odds ratio (OR): 3.06; 95% confidence interval (CI): 0.97, 9.80) and the presence of either a syringe (OR: 1.63; 95% CI: 0.54, 4.95) or drugs at the scene (OR: 9.0, 95% CI: 1.07, 410.5) were strongly correlated with testing positive for morphine.

Among free morphine concentrations, central values (LV and RV) were highest, followed by the thoracic pool, then peripheral values (FA and FV). The LV had the highest values; the FV had the lowest concentration (Table 2). A similar pattern was observed in total morphine values with central values greater than peripheral values (Table 3). Graphical comparisons in the form of side-by-side boxplots are shown in Fig. 1.

As a matter of relative concentration, free FA values were 21% higher than FV values (95% CI: 1.01–1.40). LV values were on average 88% higher than FV values (95% CI: 1.53–2.23). Among total morphine metabolite values, total FA values were 23% higher than FV values (95% CI: 0.99–1.47) and left ventricle values were 94% higher (95% CI: 1.47–2.28). Although there was a significant difference among the means of free and total femoral blood values, the medians were nearly identical.

Figures 2 and 3 plot free and total log-transformed morphine values for each decedent at the respective sampling sites. The solid lines denote the simple linear regression line for the data. The dashed lines denote the $y = x$ regression line (assuming 1 to 1 correspondence of values between sites). In general, free morphine values appear to agree slightly more than total morphine values.

Figure 4 graphically displays the effect of sampling time on both free and total morphine values. The solid lines display the predicted simple linear regression. While overall there was a trend

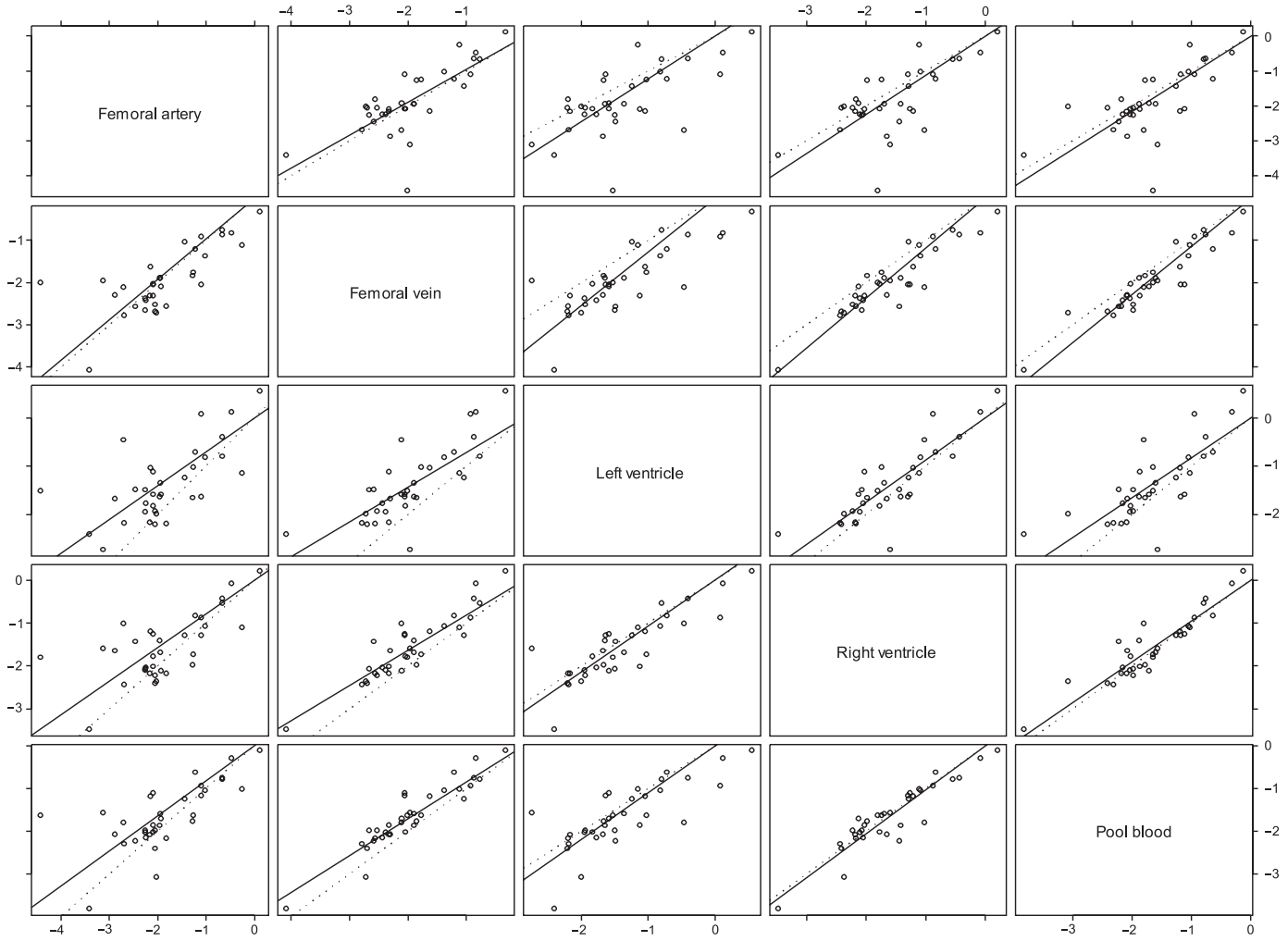

FIG. 2—*Scatterplot matrix of transformed free morphine concentrations for the sampling sites.*

toward declining morphine values over time, in no case was this effect significant (all $p > 0.20$).

While overall there was some evidence for a significant difference between the mean values at each of the sampling sites (overall free, $p = 0.079$; total, $p = 0.031$), no group stood out as significantly different from any other in post-hoc testing.

Discussion

Both free and total morphine values show marked variation among sites within the same person. We conclude that central morphine values, whether measured as free or total morphine, were higher than peripheral values. These observations are consistent with prior observations. Collection of samples from the FV will yield conservative estimates of antemortem drug values. Despite these general observations, we did not observe any statistically significant differences between the sampling sites because of large variance and small number of subjects.

Of the 76 suspected heroin overdose cases, only 44 contained a detectable concentration of morphine; the reminder died of other causes, including drugs other than opioids. Details observed at the scene of death, in particular fresh track marks and the presence of drugs at the scene, were associated with a heroin overdose. Estimation of antemortem blood drug concentrations from postmortem samples is complicated by site- and time-dependent variables. Although site-dependent differences are generally observed, these cannot be predicted with certainty in individual cases. This study not only emphasizes the difficulty in determining the postmortem morphine concentration, but also underscores the onsite determination of the role of heroin as the cause of death. Although there appears to be a small decline in morphine concentration over time, the effect was not significant (Fig. 4).

In an idyllic situation, one would theoretically compare postmortem values to an antemortem morphine (heroin) dose, using ideal specimen collection practices, in order to establish which of these postmortem specimens should correspond with antemortem values and how that relationship is affected by time of postmortem (manuscript in preparation). However, as these patients were already deceased, our goal was to establish agreement between morphine concentrations obtained at different sites. Specifically, we made comparisons of femoral venous concentrations to femoral arterial concentrations, comparisons of concentration of morphine in LV and RV and in femoral venous blood.

Besides collection site, other aspects of specimen collection may affect estimates of drug concentration. In particular, specimen volume may affect estimated blood drug concentrations. Drawing large samples from a single site (≥ 10 mL) may drain that site's vascular reservoir of regional blood. Continued aspira-

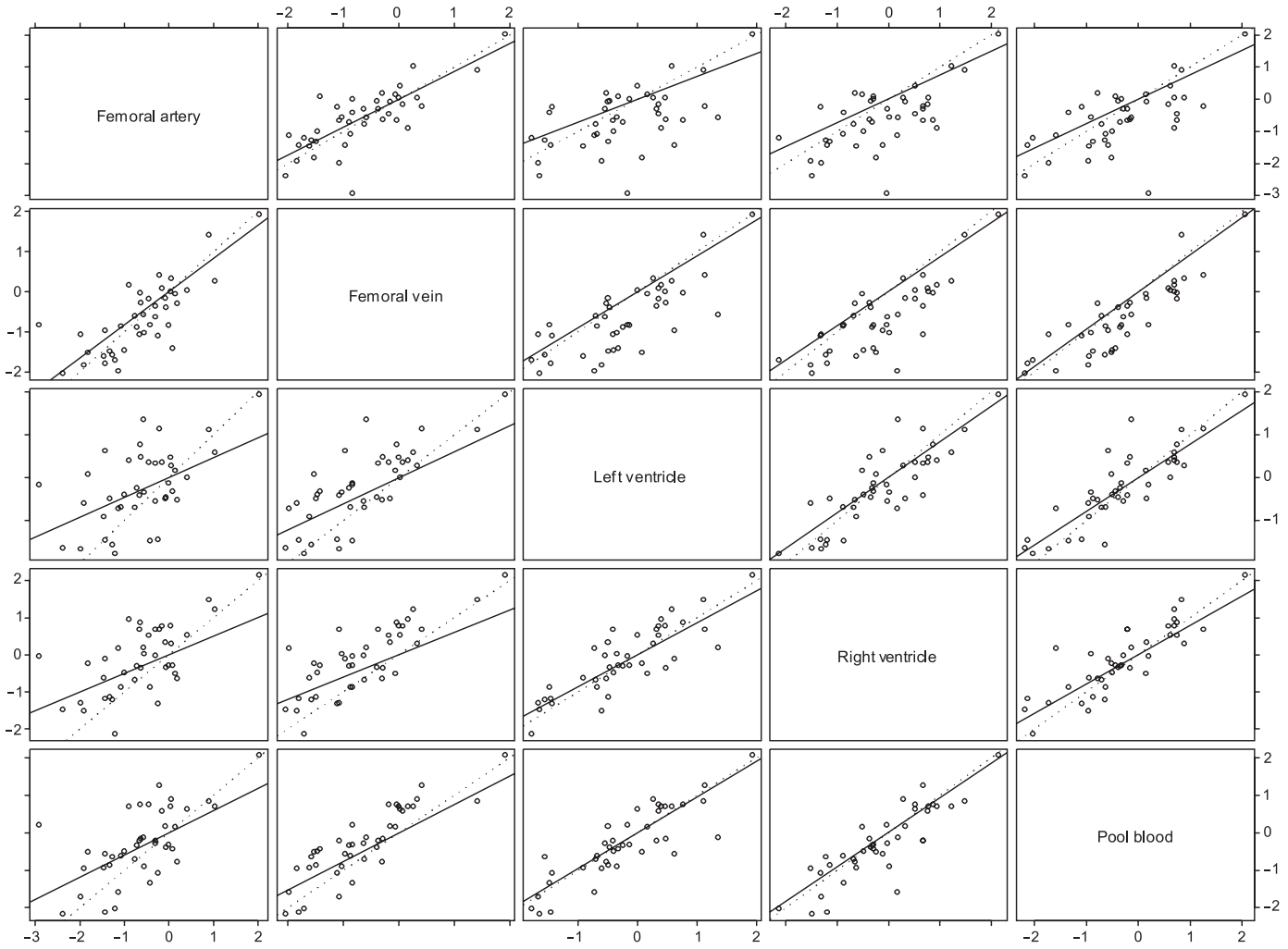

FIG. 3—*Scatterplot matrix of transformed total morphine concentrations for the sampling sites.*

tion may result in blood permeating from central sites, thus contaminating forensic samples. Thus, a large femoral aspiration may also contain iliac or inferior vena cava blood, or a ventricular aspiration could also draw blood from the pulmonary artery or vein, aorta or vena cava. Although uniform sample collection protocols may be advantageous from a data comparison standpoint, they may not be practical from a forensic standpoint. This study shows that even when collection protocols are rigorously designed to ensure sample integrity, considerable variability still exists.

Some of the variability observed in the sample values may also be attributed to a lack of postmortem stability of either the drugs or the specimens (12–13), particularly a problem for some opiates, antidepressants, antipsychotics, and benzodiazepines (13). A number of postmortem factors affect the concentration of a drug in specimens. These include postmortem redistribution for drugs, especially those with high volume of distribution. Consequently, any site-dependent change in concentration is relevant to the interpretation of concentration and drug effects (13–14). We observed an insignificant decline in concentration as the postmortem interval increased (Fig. 4). Given that this decline was consistent over nearly all sampling sites, it is likely that our inability to observe a statistically significant difference was in part because of our relatively small sample of 44. Nonetheless, this decline appears small.

Existing data describing site differences in postmortem morphine concentrations in humans are limited. In an autopsy series, Logan and Smirnow (15) demonstrated that femoral (artery or vein not specified) and heart (left ventricular) blood free morphine concentrations were generally in agreement at lower concentrations but varied greatly at higher concentrations. As untransformed data tend to coalesce around zero and demonstrate greater variability at higher concentrations, it is possible that their conclusion is influenced by the lack of statistical correction. Log transformation substantially stabilized the variance of the values except for a limited number of extremely elevated values. However, in contrast, Gerostamoulos and Drummer (14) could not find a significant difference between subclavian, femoral (artery or vein not specified), and heart (left ventricular) blood morphine or metabolite concentrations. In general, postmortem specimens obtained centrally showed higher morphine concentrations than peripheral specimens. Many studies describing site variability in postmortem morphine concentrations omit important methodological details regarding specimen collection, not the least of which is the effect of sample size on drug concentration. Additional investigation of sample size and the effect of repeat sampling at the same site to determine the effect of blood flow from central compartments is warranted.

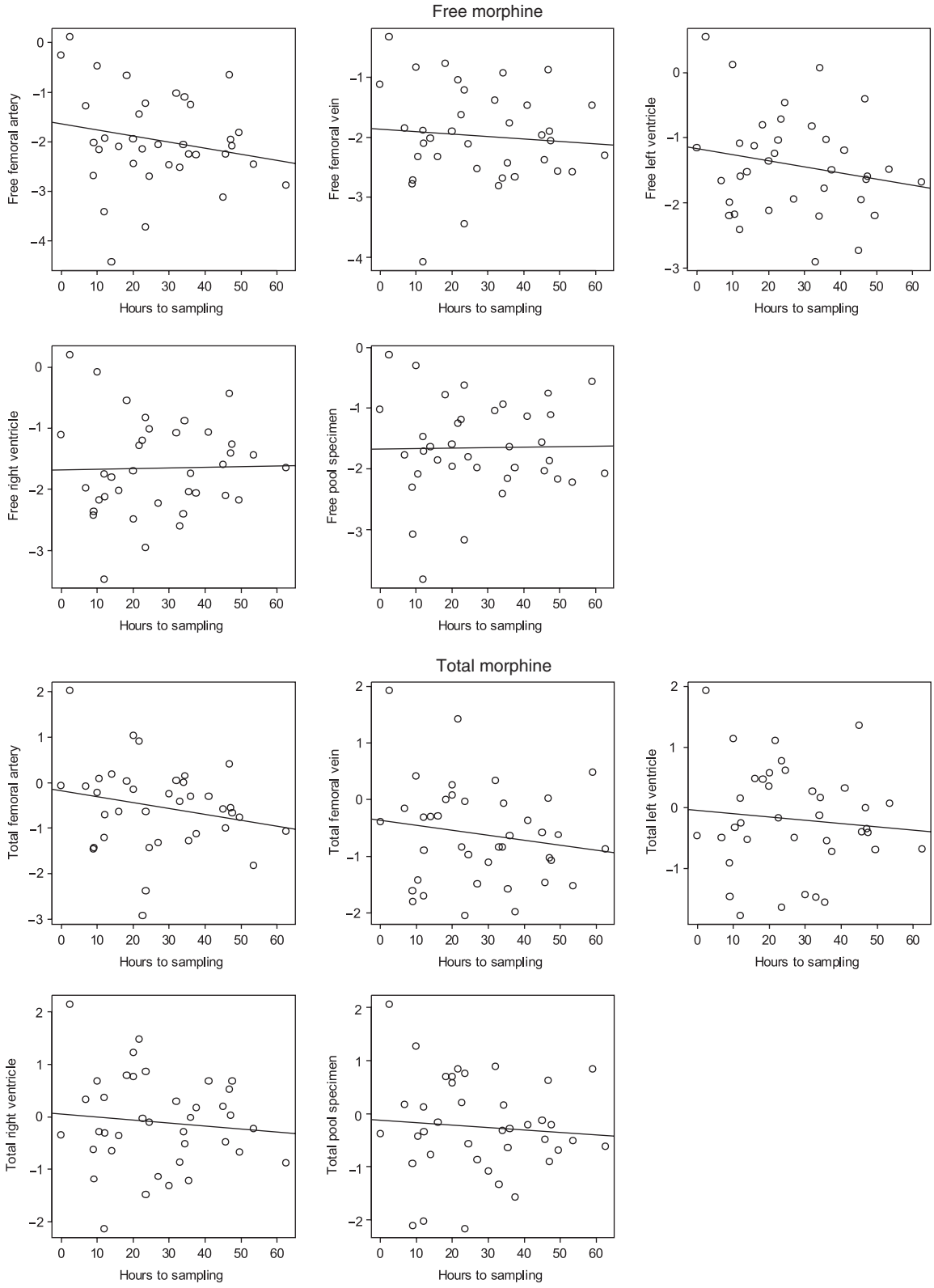

FIG. 4—*Effect of time of specimen collection on free and total transformed morphine concentrations.*

Acknowledgments

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Additional information and reprint requests:
Cameron S. Crandall, M.D.
Department of Emergency Medicine
MSC10 5560
1 University of New Mexico
Albuquerque, NM 87131-0001
E-mail: ccrandall@salud.unm.edu