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Comparison of ethanol concentrations in venous blood and end-expired breath during a controlled drinking study

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Abstract

Concentration–time profiles of ethanol were determined for venous whole blood and end-expired breath during a controlled drinking experiment in which healthy men ($n = 9$) and women ($n = 9$) drank 0.40–0.65 g ethanol per kg body weight in 20–30 min. Specimens of blood and breath were obtained for analysis of ethanol starting at 50–60 min post-dosing and then every 30–60 min for 3–6 h. This protocol furnished 130 blood–breath pairs for statistical evaluation. Blood-ethanol concentration (BAC, mg/g) was determined by headspace gas chromatography and breath-ethanol concentration (BrAC, mg/2 l) was determined with a quantitative infrared analyzer (Intoxilyzer 5000S), which is the instrument currently used in Sweden for legal purposes. In 18 instances the Intoxilyzer 5000S gave readings of 0.00 mg/2 l whereas the actual BAC was 0.08 mg/g on average (range 0.04–0.15 mg/g). The remaining 112 blood- and breath-alcohol measurements were highly correlated ($r = 0.97$) and the regression relationship was BAC $= 0.10 + 0.91$BrAC and the residual standard deviation (S.D.) was 0.042 mg/g (8.4%). The slope (0.91 ± 0.0217) differed significantly from unity being 9% low and the intercept (0.10 ± 0.0101) deviated from zero ($t = 10.2$, $P < 0.001$), indicating the presence of both proportional and constant bias, respectively. The mean bias (BAC − BrAC) was 0.068 mg/g and the 95% limits of agreement were −0.021 and 0.156 mg/g. The average BAC/BrAC ratio was 2448 ± 540 (±S.D.) with a median of 2351 and 2.5th and 97.5th percentiles of 1836 and 4082. We found no significant gender-related differences in BAC/BrAC ratios, being 2553 ± 576 for men and 2417 ± 494 for women ($t = 1.34$, $P > 0.05$). The mean rate of ethanol disappearance from blood was 0.157 ± 0.021 mg/(g per hour), which was very close to the elimination rate from breath of 0.161 ± 0.021 mg/(2 l per hour) ($P > 0.05$). Breath-test results obtained with Intoxilyzer 5000S (mg/2 l) were generally less than the coexisting concentrations of ethanol in venous blood (mg/g), which gives an advantage to the suspect who provides breath compared with blood in cases close to a threshold alcohol limit.

Keywords: Alcohol; Analysis; Blood; Breath; Drunk driving; Ethanol; Intoxilyzer 5000S; Pharmacokinetics

1. Introduction

Breath-alcohol instruments are widely used for testing alcohol-impaired drivers both at the roadside for orientation purposes (screening tests) and also for evidential purposes when the results are used for prosecution [1–5]. Most countries in Europe have introduced threshold concentration limits of alcohol in a person's breath (e.g. 0.10 and 0.25 mg/l) and these operate alongside the more well established blood-ethanol concentration limits (e.g. 0.20 and 0.50 mg/g) [6]. This legal framework avoids the need to translate the result of an evidential breath-alcohol test into the presumed coexisting blood-ethanol concentration [1–3]. Discussion and debate about the actual BAC/BrAC ratio for any individual subject and any variations from time-to-time are redundant because the critical BrAC is defined by statute.

Although, many studies have shown high correlations ($r = 0.95–0.98$) between the concentrations of ethanol determined in blood and breath when specimens are taken nearly simultaneously, much less information exists about

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the pharmacokinetics of ethanol derived from analyzing a series of breath samples [3,7]. The closeness of agreement between blood- and breath-alcohol concentration profiles during absorption, distribution and elimination stages of ethanol metabolism deserve further investigation. In forensic casework, it is sometimes necessary to make forward or retrograde extrapolations of a suspect's blood- or breath-alcohol concentration, e.g. from the time of sampling back to the time of driving [8–10]. To increase confidence in making such forensic calculations, more information is needed about the pharmacokinetics of ethanol in end-expired breath compared with venous blood.

Here we present the results of a controlled study of the concentrations of ethanol determined in blood and end-expired breath with focus on the agreement between concentration–time profiles of ethanol in these two biological media. The quantitative relationship between BAC and BrAC was evaluated by two different statistical methods, namely correlation–regression analysis [11,12] and the method of differences proposed by Bland and Altman [13–15].

2. Materials and methods

2.1. Subjects and conditions

Healthy volunteers consisting of nine men with mean age 41 years and mean body weight 80.6 kg and nine women with mean age 36.7 years and mean body weight 64.3 kg volunteered to participate in the study after information was given about the aims and risks involved. Most subjects drank neat whisky (40% (v/v)) although a few chose white wine (9.6% (v/v)) in amounts calculated to provide 0.40–0.65 g ethanol per kg body weight. The drinks were consumed within 20–30 min and each subjects started drinking at 10 min intervals.

2.2. Blood sampling and determination of ethanol

Venous blood samples were taken from an indwelling catheter at exactly timed intervals after the start of drinking (60, 90, 120, 150, 180, 240, 300, and 360 min). Venous blood was drawn into Vacutainer tubes containing 100 mg NaF and 20 mg EDTA as preservatives. Two tubes were filled at each time point and aliquots for determination of ethanol were taken from both tubes. The mean of triplicate determinations by headspace gas chromatography was used to plot concentration–time profiles and to compare with the breath-alcohol concentrations. The precision (standard deviation S.D.) of ethanol analysis remained more or less constant between 0 and 0.5 mg/g increasing thereafter as the concentration of ethanol increased. At a mean ethanol concentration of 0.8 mg/g, the S.D. was 0.006 mg/g, which corresponds to a coefficient of variation of 0.75% indicating high analytical precision [16]. The limit of quantitation of blood-ethanol concentration in this research study was 0.01 mg/g.

2.3. Breath-alcohol analysis

The Intoxilyzer 5000S is a quantitative infrared (IR) breath-analyzer originating from USA and manufactured by CMI Inc., Owensbro, Kentucky with Nanopuls AB, Uppsala as the Swedish representative. The Intoxilyzer 5000S has been approved for use by the Swedish police authorities for testing drunk drivers since 1989. Four Intoxilyzer 5000S instruments were borrowed from the police for use in this study. They were placed in the same large room and each unit had a wet-batch simulator device attached for control of calibration as when drunk drivers are being tested. The concentration of ethanol in breath is determined by monitoring the absorption of IR radiation at three wavelengths (3.48, 3.39 and 3.80 μM). The Intoxilyzer 5000S is used worldwide for law enforcement purposes particularly in USA and will therefore not be described in any more detail [7,17].

The subjects provided breath samples in random order into one of the four Intoxilyzer 5000S instruments according to a fixed time schedule. Each subject made a prolonged deep exhalation into the heated inlet-tube of the instrument for at least 6 s. Duplicate determinations were made 1–2 min apart and as close as possible to the time of sampling blood. During each test, room-air blanks were analyzed and accuracy of the instrument was verified by running wet-bath simulator tests before and after testing the subject. The target value of the ethanol concentration in the simulator effluent was 0.50 mg/l (acceptable tolerance 0.47–0.53 mg/l). The mean of duplicate breath-alcohol determinations (mg/2 l) was used to plot concentration–time profiles and to compare with the mean of a triplicate blood-alcohol determination (mg/g). The present version of the Intoxilyzer 5000S is preset to give zero readings (0.00 mg/l) when the actual breath-alcohol concentration is 0.03 mg/l or less, which is therefore the limit of quantitation with this instrument.

2.4. Statistical analysis

Concentration–time profiles of ethanol were plotted for each subject and the rates of disappearance of ethanol from blood and breath were determined as described by Widmark [18]. This entails inspecting each curve and fitting a straight line to the post-absorptive portions usually beginning at 90 min post-dosing. By extrapolation, the y-intercept (C_0) and the x-intercept (time_0) are determined, which correspond to the concentrations of alcohol in blood and breath if absorption and distribution of the dose was instantaneous and the times needed to reach zero ethanol concentration, respectively. The rates of elimination of ethanol from blood and breath were compared by Student's t-test [19].

The statutory alcohol limits for motorists in Sweden are 0.20 mg/g in blood and 0.10 mg/l in breath, which corresponds

to a 2100:1 blood-to-breath relationship. This follows because 0.20 mg ethanol per gram blood is equivalent to 0.21 mg ethanol per ml blood assuming the specific gravity of whole blood is 1.055. To allow direct comparisons between blood- and breath-ethanol concentrations and making plots on the same scale Intoxilyzer 5000S readings were reported as mg/2 l.

In the linear regression analysis, BrAC was chosen as independent (x-variate) and BAC as dependent (y-variate). The slope and intercept of the regression line indicates presence of proportional and constant bias between BAC and BrAC, respectively and random variation is given by the residual standard deviation [11,12].

Bland and Altman's method [13–15] was also used to compared results by the two methods of measurements. This entails plotting the individual differences against the average of them and looking for a trend. The mean and standard deviation of the individual BAC − BrAC differences are indicators of bias (accuracy) and random variations, respectively. The mean and S.D. of the differences are then used to calculate the 95% limits of agreement and the associated confidence limits as follows:

$$\text{bias} + 1.96\,\text{S.D.} \pm 1.96\left(\frac{3\text{S.D.}^2}{N}\right)^{1/2}$$

$$\text{bias} - 1.96\,\text{S.D.} \pm 1.96\left(\frac{3\text{S.D.}^2}{N}\right)^{1/2}$$

In the above equations, bias is simply the mean difference (BAC – BrAC) and S.D. is the standard deviation of the differences. Most of the differences between BAC and BrAC (95%) should be within the interval ±1.96S.D. and these are called the limits of agreement. However, these limits are subject to uncertainty and a 95% confidence interval was calculated as described by Bland and Altman [15], being $\pm 1.96\ (3\text{S.D.}^2/N)^{1/2}$.

3. Results

3.1. Pharmacokinetic profiles of ethanol in blood and breath

Fig. 1 shows the concentration–time profiles of ethanol in venous blood and end-expired breath for each of the 18 volunteer subjects. These curves follow a similar time course showing the absorption, distribution and elimination stages of alcohol metabolism. At the first sampling point 50–60 min post-drinking, the Intoxilyzer 5000S results (mg/2 l) agreed well with venous blood-ethanol (mg/g) and in a few instances BrAC was higher than BAC. At all later times for up to 6 h post-drinking the results with Intoxilyzer 5000S (mg/2 l) were always lower than the corresponding venous blood-ethanol concentrations (mg/g). Moreover, the Intoxilyzer 5000S gave zero readings (0.00 mg/2 l) in 18 cases when the actual venous BAC was 0.08 mg/g on average (range 0.04–0.15 mg/g).

Table 1
Disappearance rates of ethanol from blood and breath in male ($n = 9$) and female ($n = 9$) subjects who drank 0.40–0.65 g ethanol per kg as neat whisky or white wine in 30 min

Subjects	Disappearance rate of alcohol from blood (mg/(g per hour))	Disappearance rate of alcohol from breath (mg/(2 l per hour))
Male ($n = 9$)	0.155 ± 0.018[a]	0.150 ± 0.012[a,b]
Female ($n = 9$)	0.160 ± 0.025	0.173 ± 0.022[b]
Male and female ($n = 18$)	0.157 ± 0.021	0.161 ± 0.021[b]

Values shown are mean ± S.D.
[a] Significantly different from females, $P < 0.05$.
[b] No significant differences between elimination rates from blood and breath, $P > 0.05$.

Table 1 compares the rates of ethanol disappearance from blood and breath for all 18 subjects and also for the men and women separately. The rate of elimination of ethanol was slightly faster in women compared with men ($P < 0.05$) but no significant differences were noted when the rates of disappearance from blood and breath were compared; mean (±S.D.) 0.157 ± 0.0214 mg/(g per hour) for blood and 0.0161 ± 0.0210 mg/2 l per hour for breath ($P > 0.05$).

3.2. Duplicate breath-alcohol measurements

Fig. 2 shows a scatter plot of duplicate breath-alcohol measurements indicating a high correlation ($r = 0.99$). The regression equation was BrAC-2 = −0.001 + 1.007 BrAC-1 and the low residual S.D. of 0.011 mg/l indicates almost perfect 1:1 agreement. About 95% of differences between BrAC-1 and BrAC-2 were within ± 0.022 mg/l (1.96 × 0.011) and the S.D. of a single determination of breath alcohol concentration with the four Intoxilyzer instruments was 0.007 mg/l (coefficient of variation 3.2%).

3.3. Regression of blood- on breath-alcohol concentration

Fig. 3 is a scatter plot displaying blood-alcohol concentration (y-variate) and breath–alcohol concentration (x-variate) for all measurements. There was a high correlation coefficient $r = 0.97$, which means that 94% (r^2) of the variance in BAC is explained by the linear regression on BrAC. Other important statistics are the slope 0.91 ± 0.021 (ideally equal to unity) indicating these examples of the Intoxilyzer 5000S read low by about 9% on average ($t = 4.2$, $P < 0.001$). The y-intercept was 0.104 ± 0.010 mg/g (ideally equal to zero) indicating also a constant bias ($t = 10.2$, $P < 0.001$) and verifying that when Intoxilyzer 5000S indicates zero BrAC (0.00 mg/2 l) measurable amounts of ethanol are still present in venous blood. From the regression equation and the residual S.D., it can be shown that at a mean

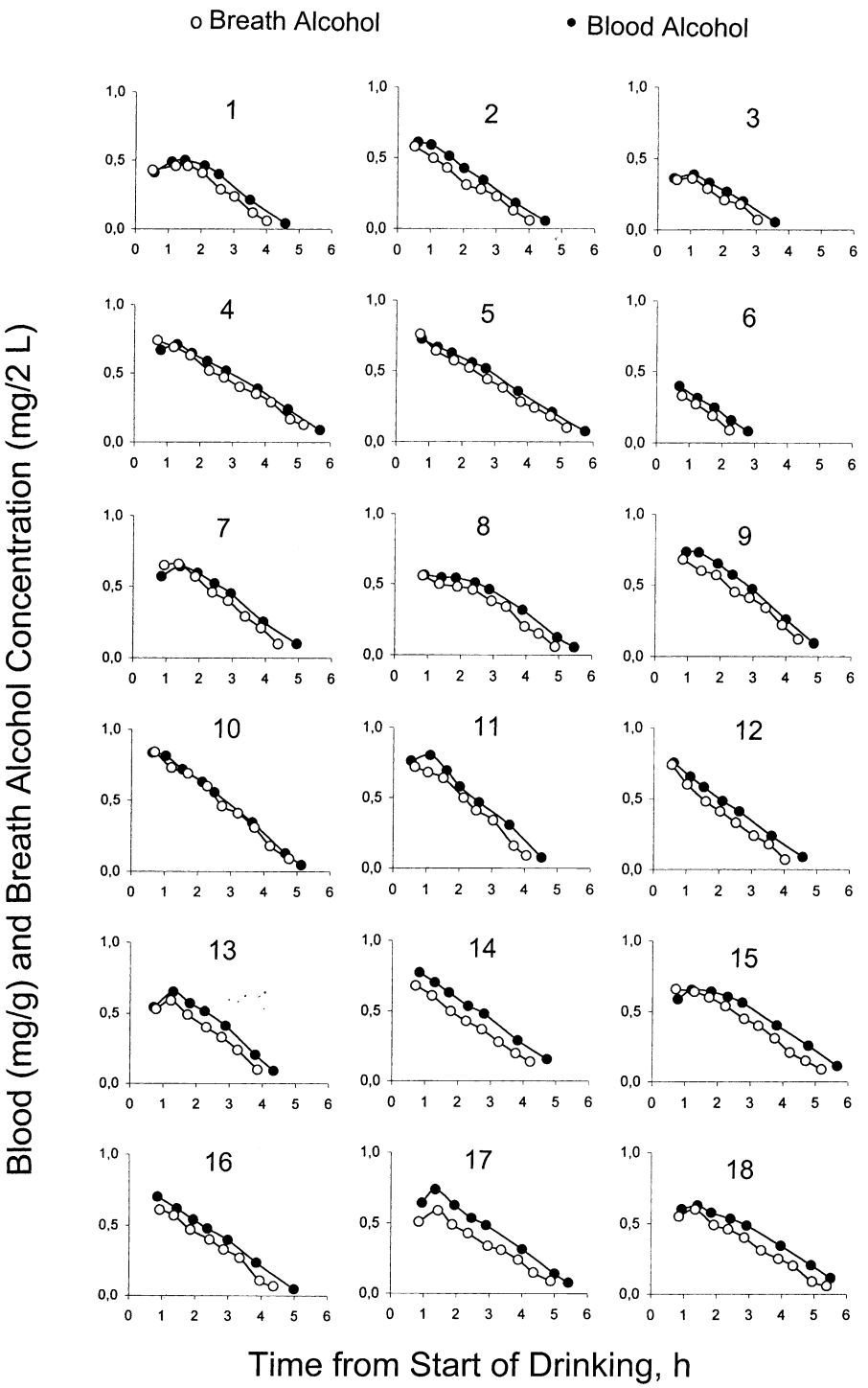

Fig. 1. Pharmacokinetic profiles of ethanol in venous whole blood (●) and end-expired breath (○) for 18 volunteer subjects who drank a moderate amount of alcohol (0.40–0.65 g/kg).

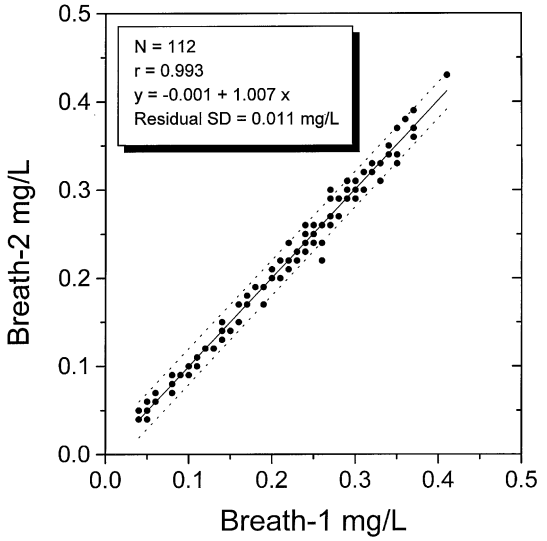

Fig. 2. Association between duplicate breath-alcohol measurements, where N is number of x–y pairs, r is the correlation coefficient and S.D. is residual standard deviation or random error. The regression equation was BrAC-2 = −0.001 + 1.007 BrAC-1.

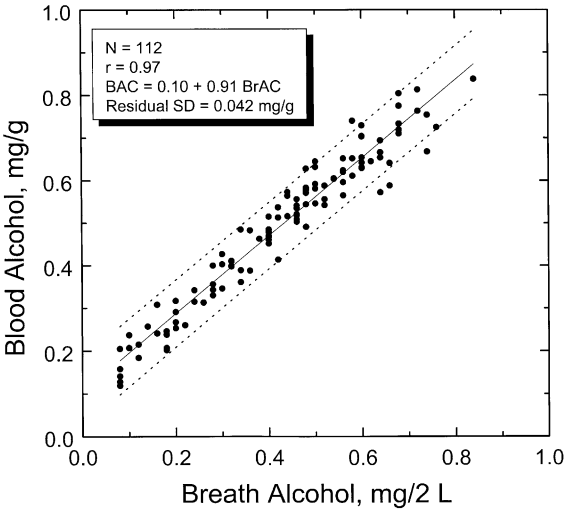

Fig. 3. Scatter plot of venous blood-alcohol (x-variate mg/g) and breath-alcohol (y-variate mg/2 l), where N is number of x–y pairs, r is the correlation coefficient, residual S.D. is residual standard deviation or random error.

BrAC of 0.50 mg/2 l, the expected venous BAC will be 0.56 mg/g and could range from 0.48 to 0.64 mg/g in 95 times of 100.

A correlation–regression analysis was also done using the blood–breath data for individual subjects with 6–7 paired samples of BAC and BrAC included. The correlation coefficients were high ($r = 0.95$–0.99) and the regression coefficients were always less than unity indicating proportional bias.

3.4. Differences between blood- and breath-alcohol concentration

Fig. 4 illustrates a Bland and Altman plot with the difference between results (BAC − BrAC) plotted against the mean concentration of ethanol (BAC + BrAC)/2. The observed bias was 0.068 mg/g and the S.D. of differences was 0.0452 mg/g so that the 95% limits of agreement between for results by these two methods of measurement

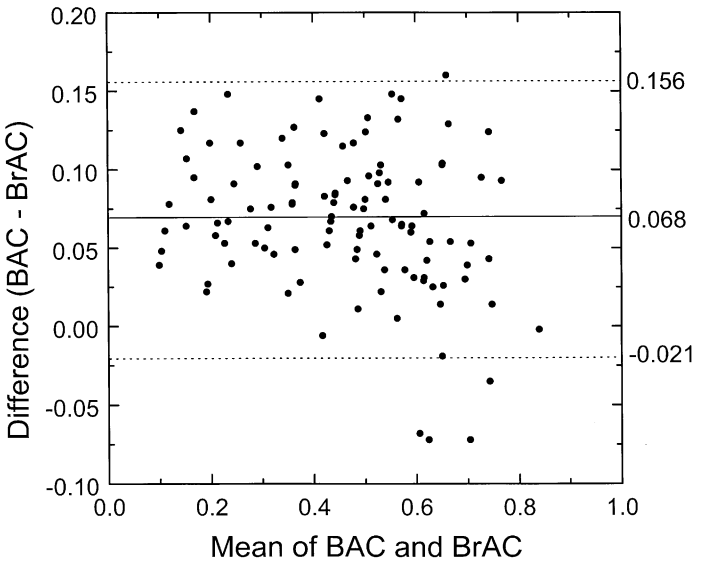

Fig. 4. Bland and Altman plot of individual differences (BAC − BrAC) against the average of the two measurements (BAC + BrAC)/2. The horizontal dotted lines show mean bias 0.068 and 95% limits of agreement (LOA) −0.021 and 0.156.

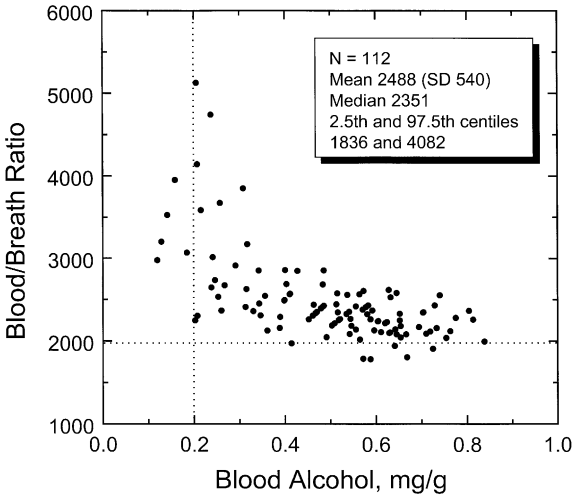

Fig. 5. Plot of blood/breath ratios of alcohol against blood-alcohol concentration, showing a curvilinear relationship with abnormally high values at low BAC (< 0.2 mg/g) shown by the dotted lines. The points appearing below the dotted horizontal line indicate blood/breath ratios of ethanol of 2000:1 or less.

are −0.021 and 0.156 mg/g (see Fig. 4). Accordingly, when the Intoxilyzer 5000S is used to estimate venous blood-alcohol concentration the results will tend to be too low with a mean bias of 0.068 mg/g and 95% of values being between 0.156 mg/g low and 0.02 mg/g high. The 95% confidence intervals for these limits of agreement (shown in brackets) were 0.156 (0.141–0.171) and −0.021 (−0.035–0.006).

3.5. Blood/breath alcohol ratios

The blood/breath ratios of alcohol varied both between subjects and within the same subject as a function of sampling time after drinking (Fig. 5). The mean ratio was 2488 (S.D. 540) with a median value of 2351 and 2.5th and 97.5th centiles of 1836 and 4082. Accordingly, about 2.5% of tests are likely to have a blood/breath ratio of ethanol below 1836 under the present test conditions. These low values are mainly observed during the absorption phase of ethanol kinetics in the tests made 50–60 min after the end of drinking. BAC/BrAC ratios are highest at 5–6 h after start of drinking when BAC was low and approaching zero. The mean BAC/BrAC ratio for men was 2553 (S.D. 576) and for women 2417 (S.D. 494); no statistically significant difference ($t = 1.34$, $P > 0.05$).

4. Discussion

The first instruments for breath-alcohol testing were rather primitive and these became available in the 1940s [1,3]. The results of breath-analysis furnished a fast and non-invasive way to estimate a person's blood-alcohol concentration by the use of a breath-to-blood conversion factor known as the blood/breath ratio. This blood/breath factor was used to calibrate the breath-analyzers and a value of 2100:1 became generally accepted for legal purposes to produce readings directly in BAC units [1]. However, several studies showed that the BAC/BrAC ratios tended to vary both between and within individuals and also during absorptive, distribution and elimination stages of ethanol metabolism [20–23]. Closer overall agreement between blood and breath-test results was obtained in the post-absorptive period using a 2300:1 BAC/BrAC ratio instead of 2100:1. Moreover, BAC/BrAC ratios tended to be less than 2100 shortly after drinking ended during the absorption phase of ethanol kinetics increasing to 2300:1 in the first part of the post-absorptive phase and as low BACs were reached the BAC/BrAC ratios increased further to reach 3000:1 or more [21]. A good explanation for these temporal variations in BAC/BrAC ratio stems from the fact that concentrations of ethanol in breath more closely reflects the concentration–time course in arterial blood rather than venous blood which was the specimen analyzed in the present study and also used for forensic purposes [24,25].

Many analytical and physiological variables account for uncertainty in BAC/BrAC ratios of ethanol [23]. Nevertheless, the 2100:1 factor gained acceptance in USA and Canada as well as some European countries on the understanding that it gives an advantage to the average person tested when compared with the coexisting ethanol concentration in venous blood [7,17]. In one large study aimed at comparing blood- and breath-alcohol concentrations in drinking drivers the venous BAC was underestimated by about 10% when a 2100:1 factor was used [1,3]. This suggests, among other things, that most drunk drivers are in the post-peak phase of ethanol metabolism when tested by the police.

Defining separate BAC and BrAC limits for driving avoids discussion and debate about variations in BAC/BrAC ratios in any individual case. Concentrations of ethanol in these two biological media are highly correlated and a strong dose–response relationship exists [3]. Moreover, the association between BAC and BrAC is much stronger then between various signs and symptoms of alcohol influence and the person's blood- or breath-alcohol concentration [26]. The concentrations of ethanol measured in blood and breath serve as highly objective evidence that a person has consumed excess alcohol and is over the legal limit for driving [3]. Many roadside surveys to assess the role of alcohol in traffic crashes (e.g. the Grand-Rapids study) were done using a breath-analyzer to monitor the presence of alcohol in the crash group and the control group of motorists [27]. Finally, the similar pharmacokinetic profiles of ethanol concentration measured in blood and breath (see Fig. 1) also supports the use of statutory alcohol concentration limits for each specimen separately.

At 50–60 min post-dosing, the results with Intoxilyzer 5000S agreed well with venous BAC and occasionally were

even slightly higher. These tests were probably made before alcohol was fully absorbed and distributed in all body fluids and when the arterial-venous differences in ethanol concentration was greatest [24,25]. The present study confirms that Intoxilyzer 5000S instrument almost always errs on the side of the suspect and in borderline cases this might make the difference between punishment or acquittal [20,28]. However, the closeness of agreement between BAC and BrAC depends to a large extent on the way the breath-instrument is calibrated and how the concentration units of breath- and blood-alcohol are reported.

In this study BAC was reported as mg/g and BrAC as mg/2 l, whereas many countries use mass/volume, e.g. mg/ml, g/l or g/100 ml for BAC. The BAC of 1.0 mg/g is the same as 1.055 mg/ml, owing to the density of whole blood being 1.055 on the average. The choice of concentration units for BAC (mg/g or mg/ml) needs to be considered when blood/breath ratios of alcohol are calculated and compared in different studies [29]. If a blood/breath factor of 2300:1 (e.g. mg/2.3 l) had been used in this study, the agreement between BAC and BrAC during the post-absorptive phase would have been much better but at the same time larger discrepancies would result for paired samples taken before peak BAC was reached, a time when arterial-venous differences are greatest. Most of the evidence suggests that the vast majority of drinking drivers are already in the post-peak or post-absorptive phase of ethanol kinetics when they are tested [28].

When results obtained by two different methods of analysis are compared (e.g. alcohol in blood and breath) it is common practice to construct an x–y scatter plot showing the result from the more reliable method on the x-axis as independent variable and the result with the new or test method displayed on the y-axis as dependent variable. The quantitative relationship between the two methods is obtained by linear regression and correlation analysis [19]. High correlation coefficients are sometimes interpreted to mean close agreement, although this lacks scientific foundation [13–15]. The correlation coefficient is a measure of the strength of the linear association between the two variables, which is not the same as good agreement [11,12]. Indeed, if two methods are designed to measure the same thing (e.g. ethanol), then a strong association and high correlation coefficient is expected [13]. Even if all the measurements cluster around the regression line but one method gives readings 50% higher or lower than the other, this still gives a high correlation coefficient but obviously the agreement between the methods is poor. Other problems arise when correlation coefficients and regression analysis are used in method comparison studies as discussed in detail elsewhere [13–15].

Two medical statisticians from England (Bland and Altman) have described an alternative way to evaluate method comparison studies and their approach has now gained wide acceptance and is recommended by certain scientific journals [30,31]. The mean difference between results by the two methods and the standard deviation of the differences are calculated to provide information about bias and random variations, respectively. In regression analysis, random variation between BAC and BrAC is given by the residual standard deviation, which in this study was 0.041 mg/g being in excellent agreement with the S.D. of differences (BAC − BrAC) of 0.045 mg/g.

In conclusion, the results of this controlled study show that both blood- and breath-alcohol concentration–time data can be used to make forward or backward estimations during the post-absorptive phase of ethanol kinetics. Translation of the BrAC into BAC before these projections are made is not recommended and can give misleading information because the BAC/BrAC factor is a moving target. The generally accepted rate of ethanol elimination from blood ranging from 0.10 to 0.20 mg/(g per hour) corresponds to an elimination rate of 0.10–0.20 mg/2 l breath per hour or 0.05–0.10 mg/l per hour. The evidential breath-analyzer Intoxilyzer 5000S (mg/2 l) almost always gave lower readings compared with venous blood-ethanol concentrations (mg/g) thus giving an advantage to the person being breath-tested.

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