Gasto cardíaco por ECOTT vs Fick

Parte 2: Análisis principales Gasto Cardíaco

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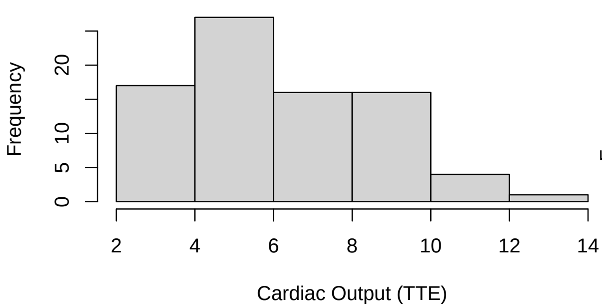
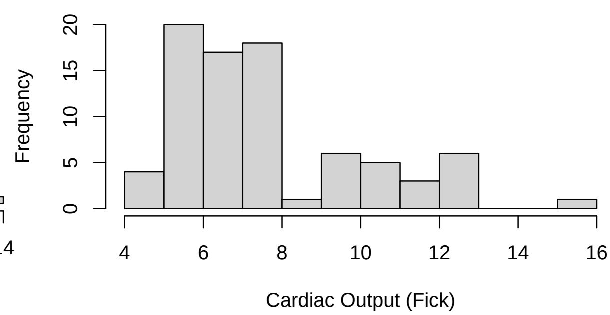
Cardiac Output

The distribution of cardiac output values for both methods is skewed as shown bellow.



(a) TTE

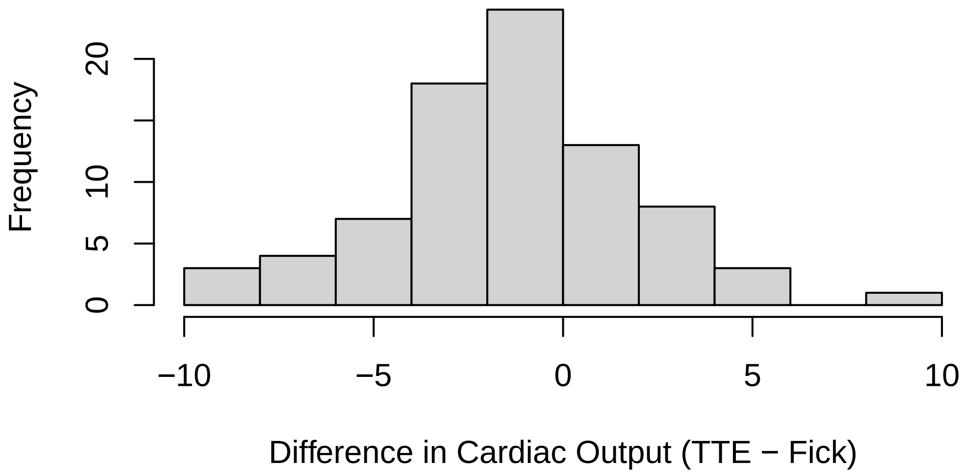


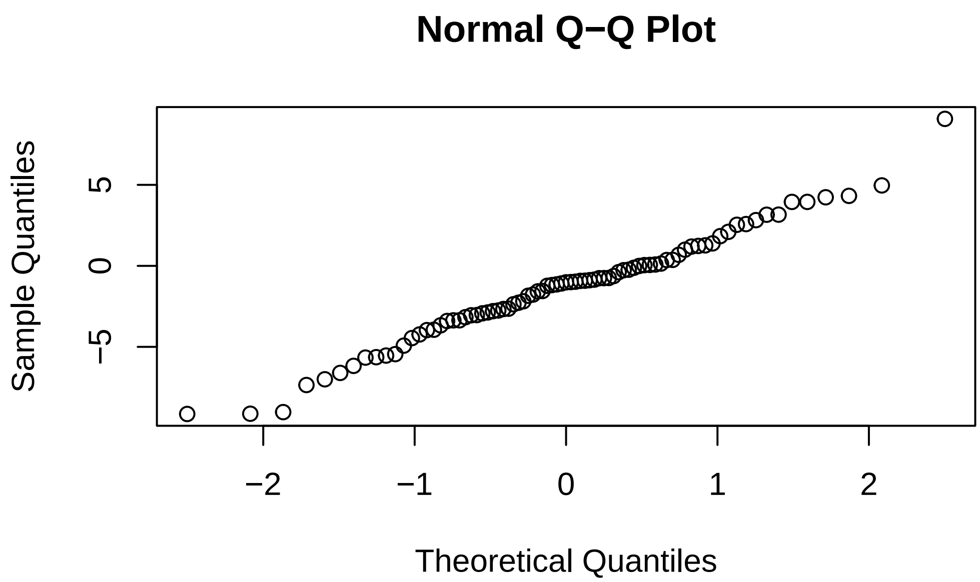
(a) Fick

Thus, bootstrapping is used to calculate the mean with 95% CI:

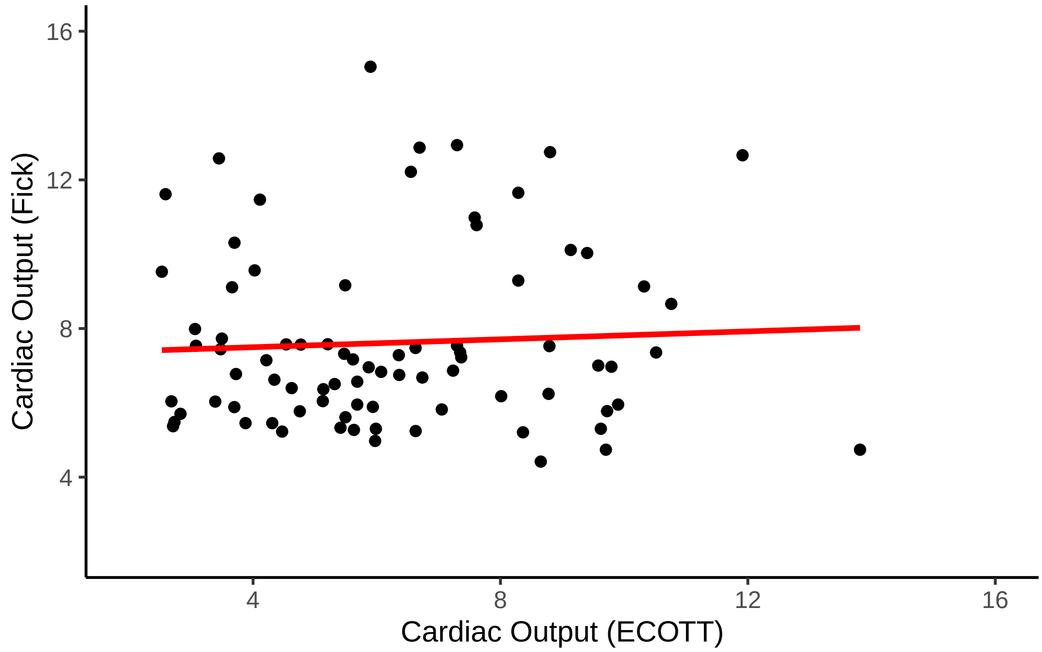
The mean cardiac output for TTE is 6.26 L/min (95% CI: 5.73 to 6.81), and for Fick, 7.62 L/min (95% CI: 7.14 to 8.18).

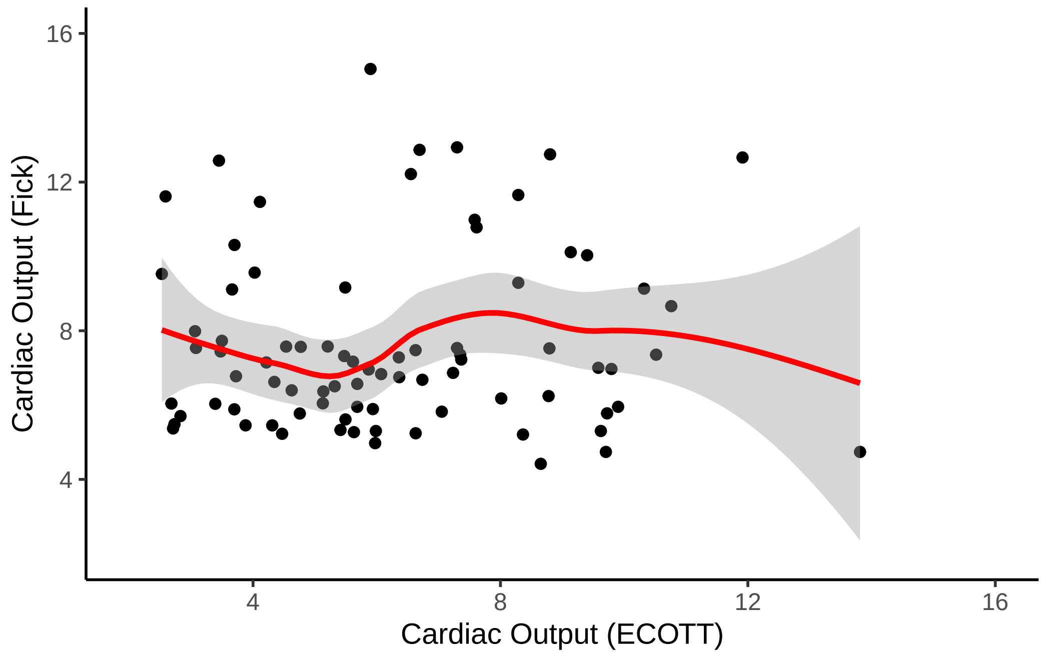
However, the distribution of differences between the two methods is approximately normal.





Assuming a linear and non-linear relationship

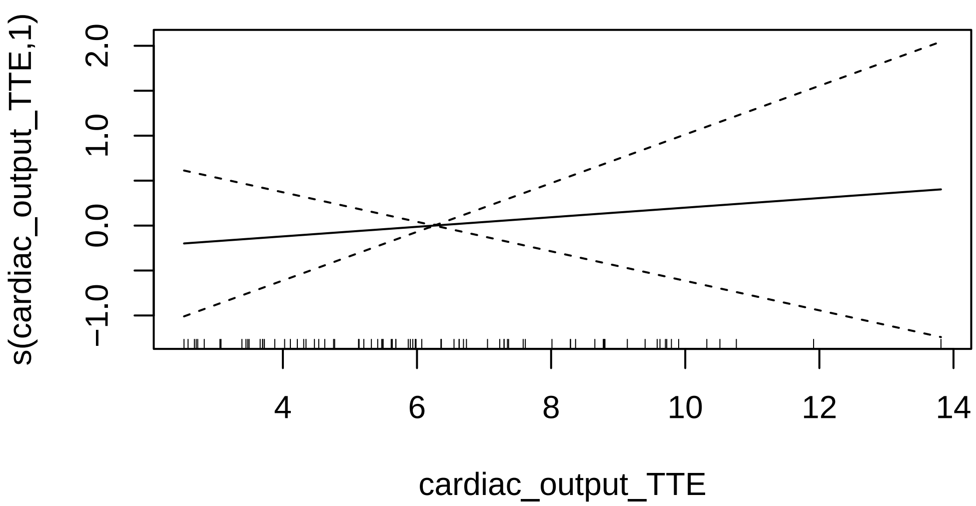




Examine if non-linear term is significantly better than linear term

```
Family: gaussian
```

```
Link function: identity

Formula:
cardiac_output_Fick ~ s(cardiac_output_TTE)

Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   7.6173     0.2674   28.49   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
                      edf Ref.df    F p-value
s(cardiac_output_TTE)   1      1 0.24   0.626

R-sq.(adj) =  -0.00959   Deviance explained = 0.303%
GCV = 5.9362  Scale est. = 5.7896    n = 81
```



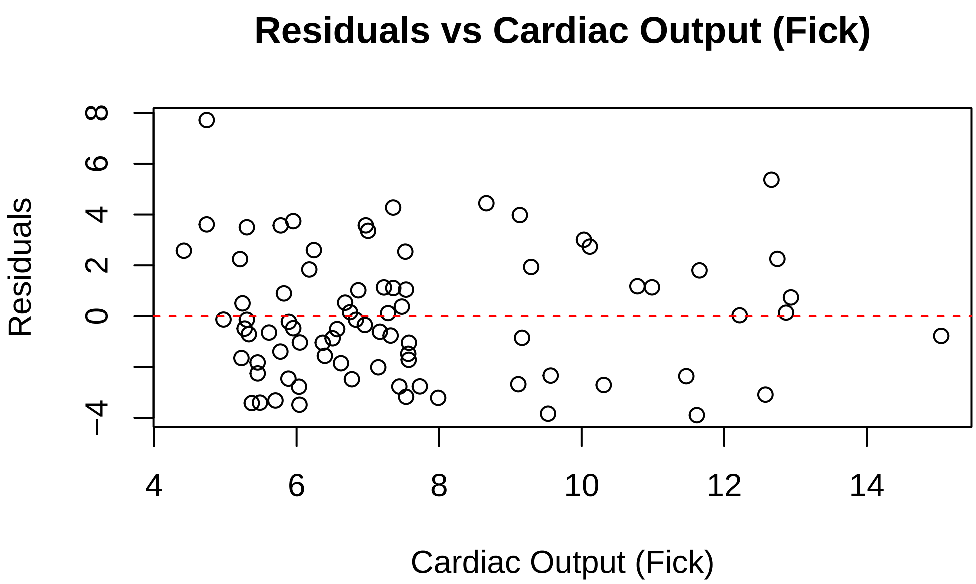
Non-linear relationship is not significantly better than linear relationship. Thus, I will model as linear relationship.

Pearson correlation

```
    Pearson's product-moment correlation

data:  data$cardiac_output_TTE and data$cardiac_output_Fick
t = 0.48997, df = 79, p-value = 0.6255
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 -0.1652936  0.2701451
sample estimates:
       cor
0.05504239
```

Linear regression

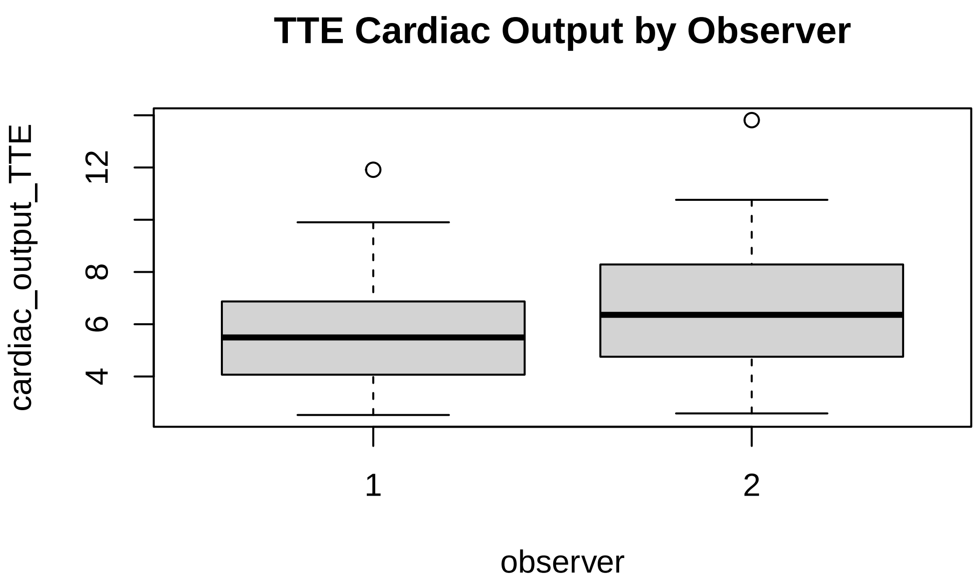
```
Call:
lm(formula = cardiac_output_TTE ~ cardiac_output_Fick, data = data)

Residuals:
    Min      1Q  Median      3Q     Max 
-3.8979 -1.8550 -0.3494  1.8022  7.7202 

Coefficients:
                    Estimate Std. Error t value Pr(>|t|)    
(Intercept)          5.82344    0.92636   6.286 1.67e-08 ***
cardiac_output_Fick  0.05688    0.11608   0.490    0.626    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 2.486 on 79 degrees of freedom
Multiple R-squared:  0.00303,	Adjusted R-squared:  -0.00959 
F-statistic: 0.2401 on 1 and 79 DF,  p-value: 0.6255
```



Linear Mixed Effects Model

```
Linear mixed model fit by REML ['lmerMod']
Formula: cardiac_output_Fick ~ cardiac_output_TTE + (1 | ID) + (1 | time_point)
   Data: data

REML criterion at convergence: 345.9

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.70612 -0.35805 -0.09272  0.25930  2.18064

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 3.170    1.780
 time_point (Intercept) 5.995    2.448
 Residual               1.240    1.114
Number of obs: 81, groups:  ID, 52; time_point, 9

Fixed effects:
                   Estimate Std. Error t value
(Intercept)         9.13612    1.18262   7.725
cardiac_output_TTE -0.01155    0.09538  -0.121

Correlation of Fixed Effects:
            (Intr)
crdc_tp_TTE -0.570
```

Would it be relevant to study the effect of the observer on the cardiac output measurements?



Test if fixed or random effect is relevant in the model.

```
Linear mixed model fit by REML ['lmerMod']
Formula: cardiac_output_Fick ~ cardiac_output_TTE + observer + (1 | ID) +
    (1 | time_point)
   Data: data

REML criterion at convergence: 341.7

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.67352 -0.37402 -0.07719  0.21721  2.13526

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 2.950    1.718
 time_point (Intercept) 6.020    2.454
 Residual               1.247    1.117
Number of obs: 81, groups:  ID, 52; time_point, 9

Fixed effects:
                    Estimate Std. Error t value
(Intercept)         9.747392   1.219317   7.994
cardiac_output_TTE -0.004353   0.094323  -0.046
observer2          -1.070272   0.566691  -1.889
```

```
Correlation of Fixed Effects:
            (Intr) c__TTE
crdc_tp_TTE -0.533
observer2   -0.258 -0.052


Linear mixed model fit by REML ['lmerMod']
Formula:
cardiac_output_Fick ~ cardiac_output_TTE + (1 | ID) + (1 | time_point) +
    (1 | observer)
   Data: data

REML criterion at convergence: 344.7

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.68490 -0.37517 -0.07848  0.23299  2.16051

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 2.9621   1.7211
 time_point (Intercept) 6.0172   2.4530
 observer   (Intercept) 0.4114   0.6414
 Residual               1.2420   1.1145
Number of obs: 81, groups:  ID, 52; time_point, 9; observer, 2

Fixed effects:
                    Estimate Std. Error t value
(Intercept)         9.194789   1.262103   7.285
cardiac_output_TTE -0.006784   0.094244  -0.072

Correlation of Fixed Effects:
            (Intr)
crdc_tp_TTE -0.527


Data: data
Models:
linear_mixed_model: cardiac_output_Fick ~ cardiac_output_TTE + (1 | ID) + (1 | time_point)
linear_mixed_model_obs_fixed: cardiac_output_Fick ~ cardiac_output_TTE + observer + (1 | ID)
                             npar    AIC    BIC  logLik -2*log(L)  Chisq Df
linear_mixed_model              5 354.77 366.74 -172.38    344.77
linear_mixed_model_obs_fixed    6 353.23 367.60 -170.62    341.23 3.5363  1
                             Pr(>Chisq)
```

```
linear_mixed_model
linear_mixed_model_obs_fixed    0.06004 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Fixed effect not statistically significant, and AIC decreases, whereas BIC does not. This suggests that the model fit does not improve importantly. I will re-check in Bland-Altman analysis if including observer would be relevant.

```
Data: data
Models:
linear_mixed_model: cardiac_output_Fick ~ cardiac_output_TTE + (1 | ID) + (1 | time_point)
linear_mixed_model_obs_random: cardiac_output_Fick ~ cardiac_output_TTE + (1 | ID) + (1 | tim
                              npar    AIC    BIC  logLik -2*log(L)  Chisq Df
linear_mixed_model               5 354.77 366.74 -172.38    344.77
linear_mixed_model_obs_random    6 355.72 370.08 -171.86    343.72 1.0532  1
                              Pr(>Chisq)
linear_mixed_model
linear_mixed_model_obs_random     0.3048
```

Random effect not relevant, as AIC and BIC do not improve, and model is not significantly better than the simpler model.

Intraclass correlation coefficient (ICC)

```
Single Score Intraclass Correlation

  Model: twoway
  Type : agreement

  Subjects = 81
    Raters = 2
  ICC(A,1) = 0.0481

F-Test, H0: r0 = 0 ; H1: r0 > 0
  F(80,81) = 1.12 , p = 0.311

95%-Confidence Interval for ICC Population Values:
 -0.139 < ICC < 0.242
```

ID	CO 1 (TTE), L/min	CO 2 (TTE), L/min	CO 3 (TTE), L/min	Mean CO TTE, L/min	CV (%)	CE (%)	CO (Fick method), L/min
1	6.41	7.24	6.24	6.63	8.02	4.63	5.24
2	14.72	13.11	13.61	13.81	5.96	3.44	4.74
2	9.93	9.87	9.31	9.70	3.52	2.03	4.74
3	3.37	3.55	3.43	3.45	2.74	1.58	12.58
3	3.95	4.10	4.03	4.03	1.83	1.05	9.57
4	2.69	2.81	2.61	2.71	3.74	2.16	5.37

CE: Coefficient of Error; CV: Coefficient of Variation; TTE: Transthoracic Echocardiography.

Coefficient of variation (CV) and coefficient of error (CE)

The following calculation is the coefficient of variation (CV) for the overall averaged measurements, expressed as percentage:

Fick CV: 31.44%

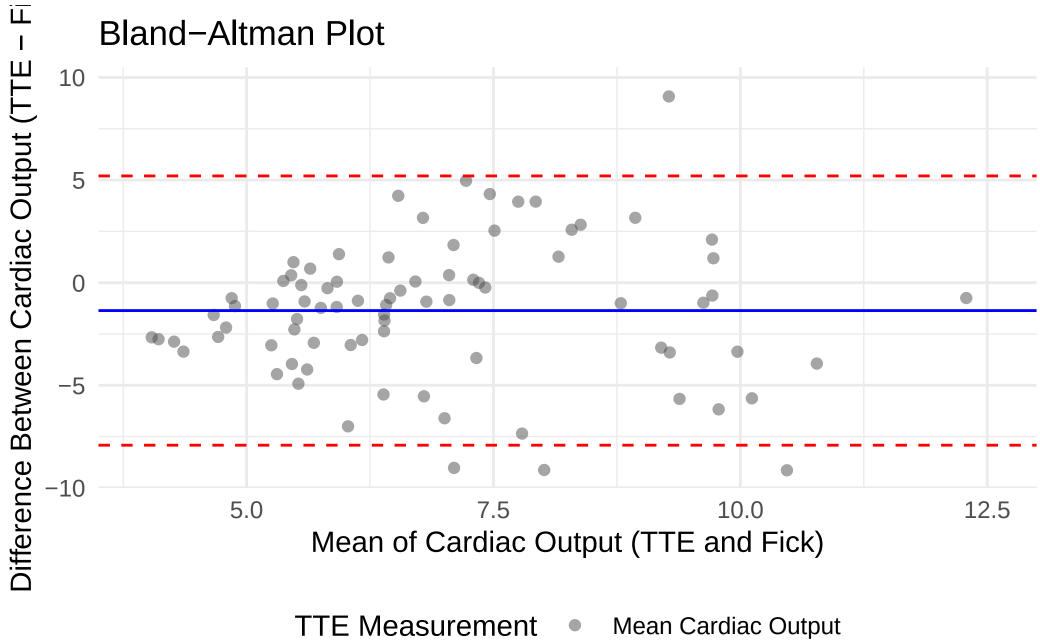
TTE CV: 39.55%

Because there are multiple measurements that are averaged to produce the mean cardiac output for TTE, we can calculate the coefficient of error (CE) as suggested by Cecconi, et al.[1] The following calculations reproduce the structure of the table in their review article:

The mean CV of TTE for the repeated measurements per patient was 7.3% (95% CI: 6.2 to 8.7) and the CE was 4.2% (95% CI: 3.6 to 5), corresponding to a precision of 8.4% (95% CI: 7.2 to 10.1).

Bland-Altman Plot

Bland Altman-single measure



Systematic bias (Paired t-test)

```
	Paired t-test

data:  data$cardiac_output_TTE and data$cardiac_output_Fick
t = -3.6582, df = 80, p-value = 0.0004534
alternative hypothesis: true mean difference is not equal to 0
95 percent confidence interval:
 -2.1007836 -0.6204367
sample estimates:
mean difference 
       -1.36061 
```

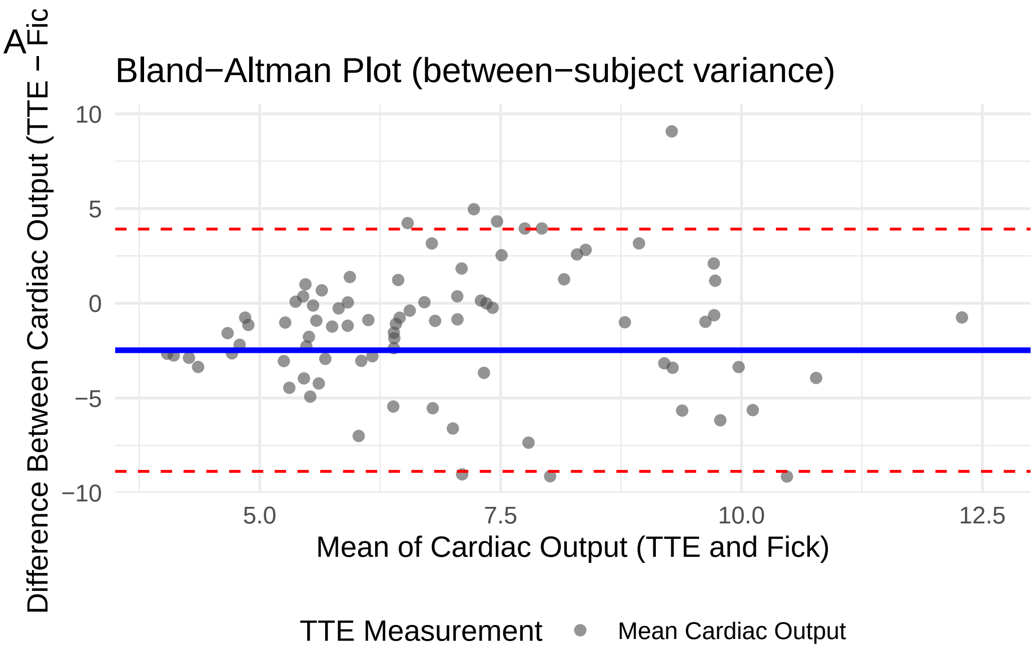
Bland Altman-repeated measures (random effects for between-subject variance)

```
Data: data
Models:
model: differences ~ 1 + (1 | ID)
model_observer: differences ~ 1 + (1 | ID) + observer
               npar    AIC    BIC  logLik -2*log(L)  Chisq Df Pr(>Chisq)
model             3 415.92 423.11 -204.96    409.92
model_observer    4 415.07 424.65 -203.54    407.07 2.8491  1    0.09143 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Despite not significantly improving the model, including observer as a fixed effect improved the distribution of observations around the mean, so this model was kept.

```
Linear mixed model fit by REML ['lmerMod']
Formula: differences ~ 1 + (1 | ID) + observer
   Data: data

REML criterion at convergence: 405.4

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.33117 -0.37765 -0.01897  0.33688  2.08532

Random effects:
 Groups   Name        Variance Std.Dev.
 ID       (Intercept) 5.647    2.376
 Residual             4.995    2.235
Number of obs: 81, groups:  ID, 52

Fixed effects:
            Estimate Std. Error t value
(Intercept)  -2.4782     0.6850  -3.618
observer2     1.4811     0.8778   1.687

Correlation of Fixed Effects:
          (Intr)
observer2 -0.780
```

A



Bland−Altman Plot (between−subject variance)
Difference Between Cardiac Output (TTE − Fic
10
5
0
−5
−10
5.0
7.5
10.0
12.5
Mean of Cardiac Output (TTE and Fick)
TTE Measurement
Mean Cardiac Output

Bland Altman-repeated measures (random effects for between-subject variance and within-subject variance)

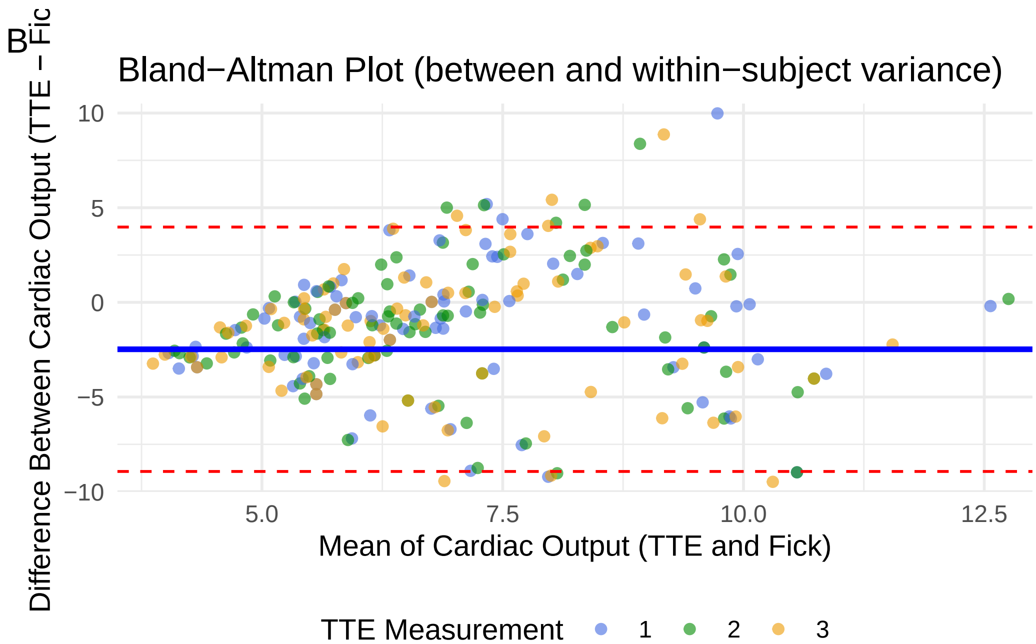
```
Data: data_long
Models:
model_long: differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement)
model_long_observer: differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement)
                    npar    AIC    BIC  logLik -2*log(L)  Chisq Df Pr(>Chisq)
model_long             5 775.39 792.86 -382.70    765.39
model_long_observer    6 774.54 795.50 -381.27    762.54 2.8491  1    0.09143 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

As before, the model with observer not significantly better, but the distribution of observations improves by including it. This, will include.

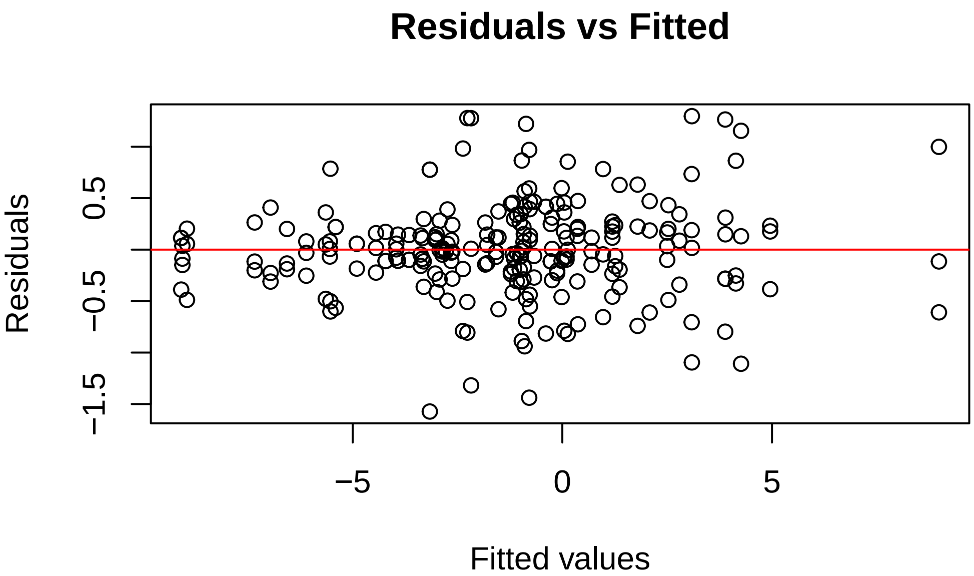
```
Linear mixed model fit by REML ['lmerMod']
Formula:
differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement) +
    observer
   Data: data_long

REML criterion at convergence: 760.9

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.85621 -0.39637 -0.02741  0.39751  2.35464

Random effects:
 Groups          Name        Variance Std.Dev.
 ID:time_point   (Intercept) 4.8936   2.2121
 ID              (Intercept) 5.6474   2.3764
 TTE_measurement (Intercept) 0.0000   0.0000
 Residual                    0.3033   0.5507
Number of obs: 243, groups:  ID:time_point, 81; ID, 52; TTE_measurement, 3

Fixed effects:
            Estimate Std. Error t value
(Intercept)  -2.4782     0.6850  -3.618
observer2     1.4811     0.8778   1.687

Correlation of Fixed Effects:
```

```
          (Intr)
observer2 -0.780
optimizer (nloptwrap) convergence code: 0 (OK)
boundary (singular) fit: see help('isSingular')
```

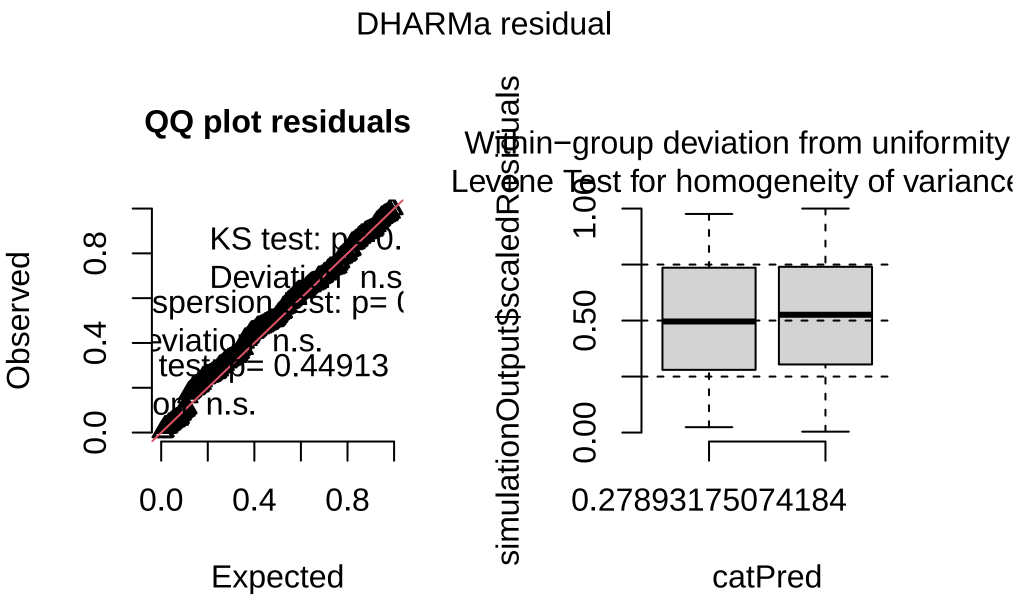
There was singularity in the prior model including a random effect for within-subject TTE measurements. Because this term is conceptually important to take into account the nested structure of the data, we will keep it in the model. Other alternatives would be to include it as a fixed effect, but this would not necessarily represent a meaningful variable to model.



Residuals and random effects diagnostics



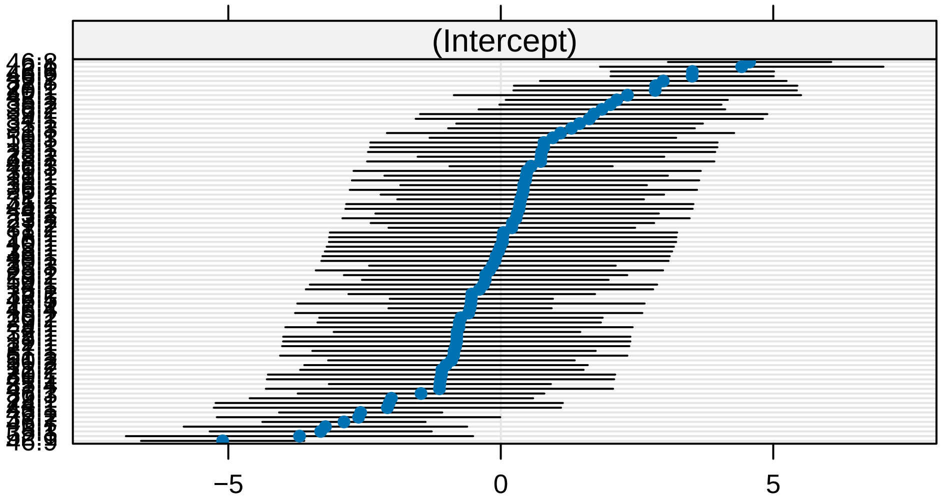
Residuals randomly distributed, no apparent patterns.



Diagnostics form predicted residuals also show random distribution, with no heteroskedasticity or patterns, supporting lineraity assumption. No evidence of influential outliers.

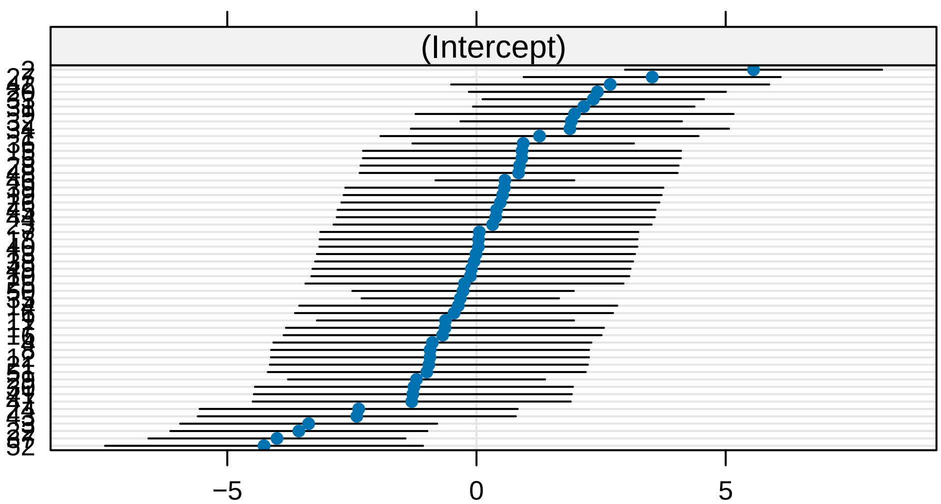
```
$`ID:time_point`
```

ID:time_point

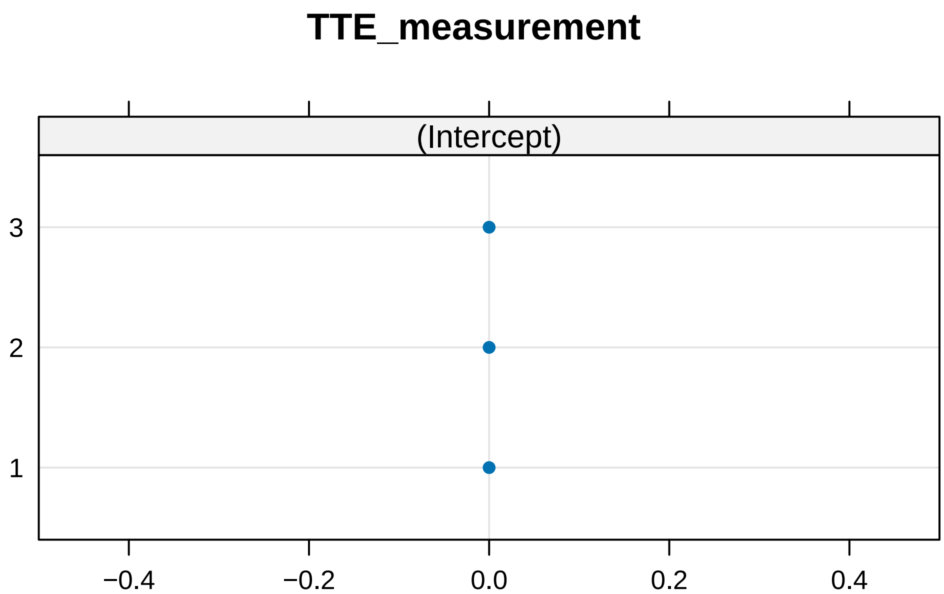



```
$ID
```

ID




```
$TTE_measurement
```



Simetric distribution, with bell curve shape, not showing strong outliers. Random effects for ID and ID:time_point relevant. For TTE measurement, no variation seen as expected due to singularity, therefore this term is not relevant for the model. As mentioned earlier, it was kept as it is considered conceptually relevant. Conclusion is that TTE measurements are quite consistent among each time point within participant.

Mean absolute difference (MAD)

The MAD for cardiac output is 2.8 (95% CI: 2 to 3.5).

Mean absolute percentage error (MAPE) and precision of Fick method

```
Precisionb (point estimate): 56.84 %
```

```
Precisionb (95% CI): 44.34 - 74.22 %
```

Summary

The mean cardiac output with TTE was 6.26 (95% CI: 5.73 to 6.81) L/min, and 7.62 L/min (95% CI: 7.14 to 8.18) for the Fick method. The correlation between the two methods was rho = 0.06 (95% CI: -0.17 to 0.27, p=0.626). In a linear mixed model with random patient slopes, there was a change in Fick CO of -0.004 (95% CI: -0.191 to 0.18) L/min for each unit change in mean TTE CO. The ICC between TCE and Fick CO 0.05 (95% CI: -0.14 to 0.24).

The mean absolute difference in CO between TTE and Fick was 2.76 (95% CI: 2 to 3.5) L/min. The coefficient of variation for an individual measurement of TTE was 39.5% and 31.44% for Fick. The mean CV of TTE for the repeated measurements per patient was 7.3% (95% CI: 6.2 to 8.7) and the CE was 4.2% (95% CI: 3.6 to 5), corresponding to a precision of 8.4% (95% CI: 7.2 to 10.1). The MAPE of the Fick method compared to TTE was 57.5% (95% CI: 45.5 - 74.6). The precision of the Fick method was 56.84% (95% CI: 44.34 to 74.22). The LSC was 11.9% (95% CI: 10.1 to 14.3) for TTE and 80.4% (95% CI: 62.7 to 105) for the Fick method.

Figure 1 shows the Bland-Altman plot for the repeated measures model with random effects for between-subject variance (Figure1A) and within-subject variance (Figure1B). The mean difference (systematic bias) between TTE and Fick CO was -2.48 (95% CI: -3.82 to -1.14, p = 0) L/min, with 95% limits of agreement of -8.93 to 3.98 L/min.

References

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