Gasto cardíaco por ECOTT vs Fick

Parte 3: Análisis Índice Cardíaco

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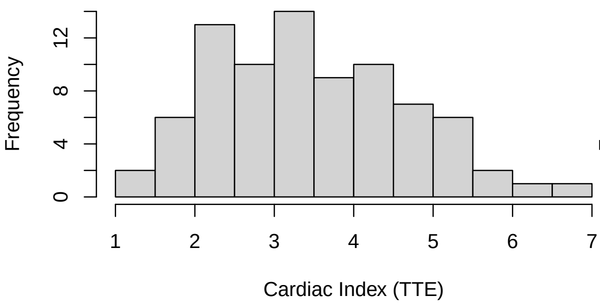
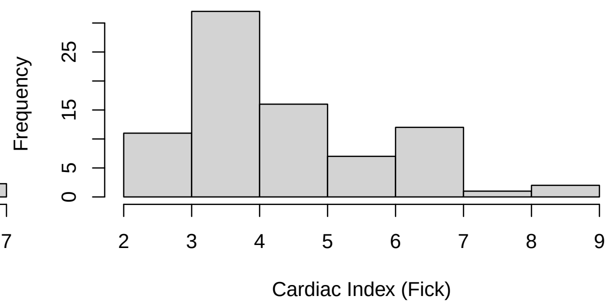
Cardiac Index

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



(a) TTE

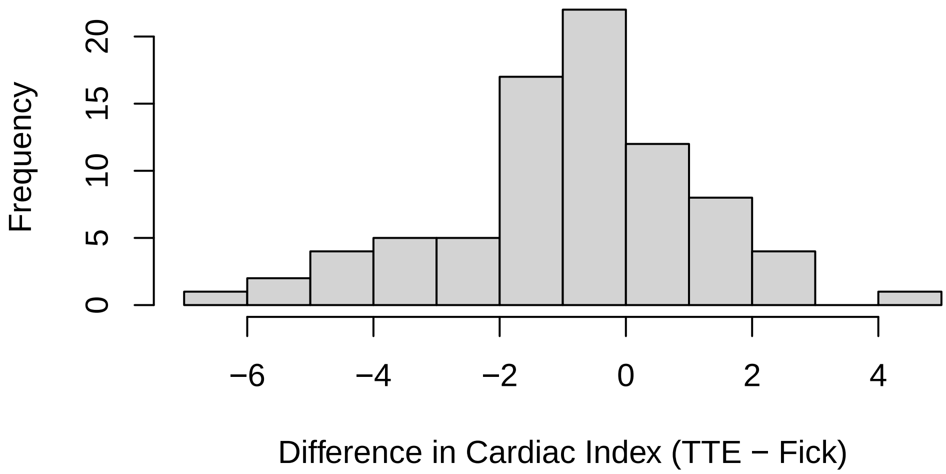


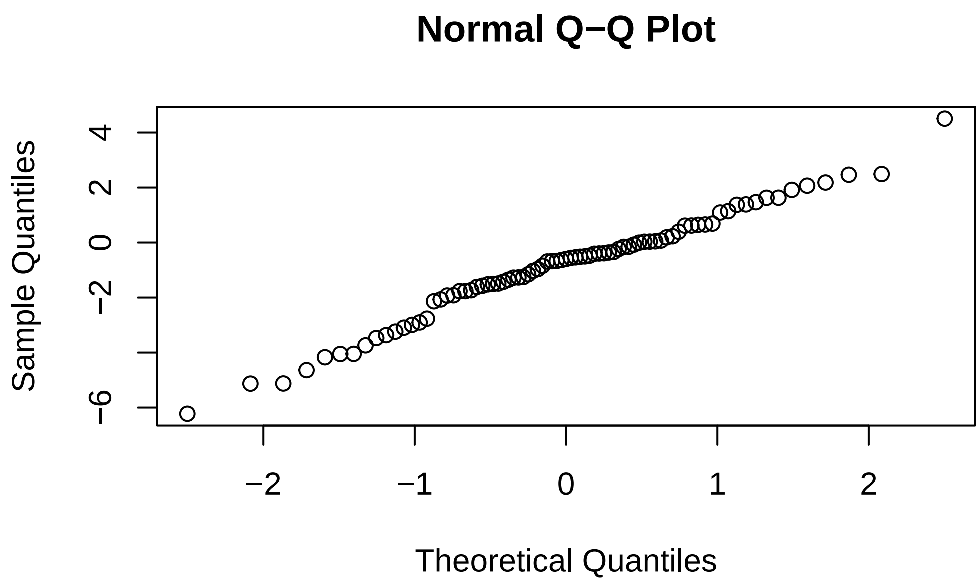
(a) Fick

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

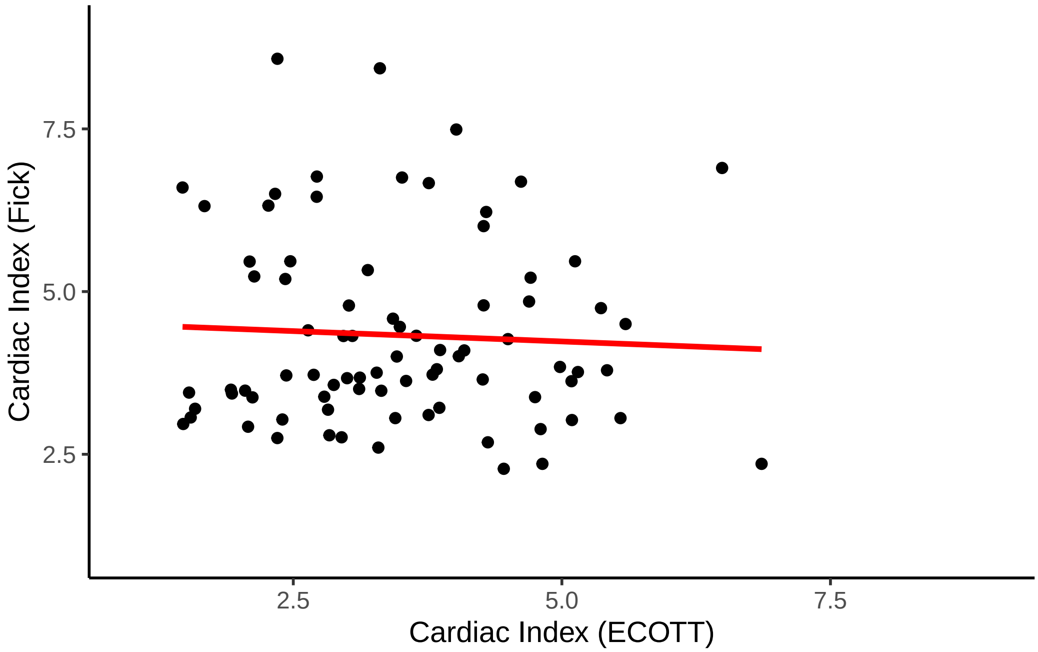
The mean cardiac index for TTE is 3.47 L/min (95% CI: 3.21 to 3.74), and for Fick, 4.33 L/min (95% CI: 4.04 to 4.67).

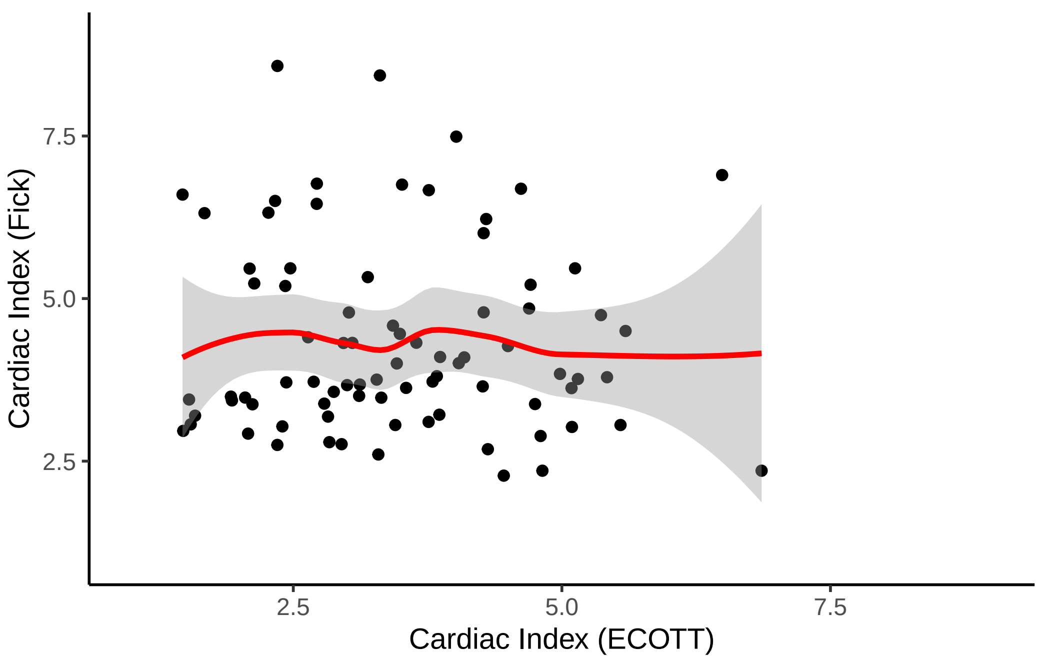
However, the distribution of differences between the two methods is approximately normal.





Assuming a linear and non-linear relationship

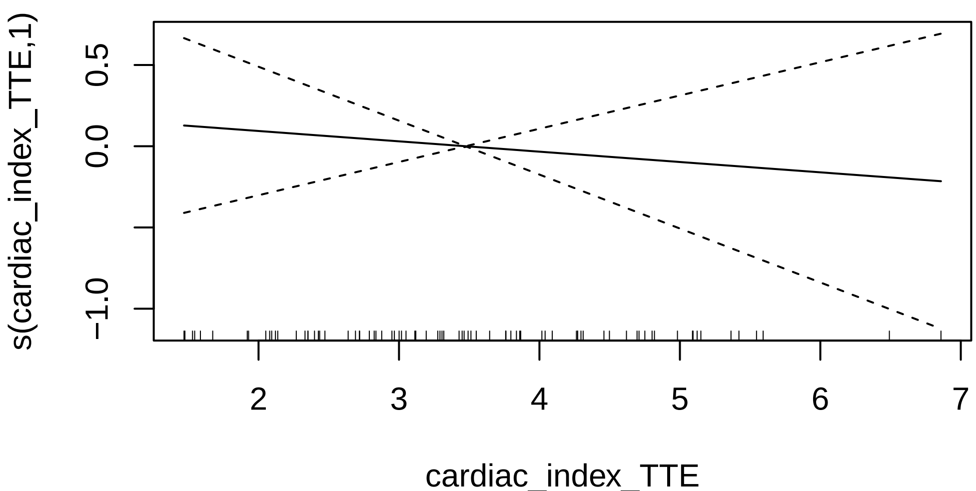




Examine if non-linear term is significantly better than linear term

```
Family: gaussian
```

```
Link function: identity

Formula:
cardiac_index_Fick ~ s(cardiac_index_TTE)

Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   4.3307     0.1621   26.72   <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_index_TTE)   1      1 0.225   0.637

R-sq.(adj) =  -0.00978   Deviance explained = 0.284%
GCV = 2.1819  Scale est. = 2.128     n = 81
```



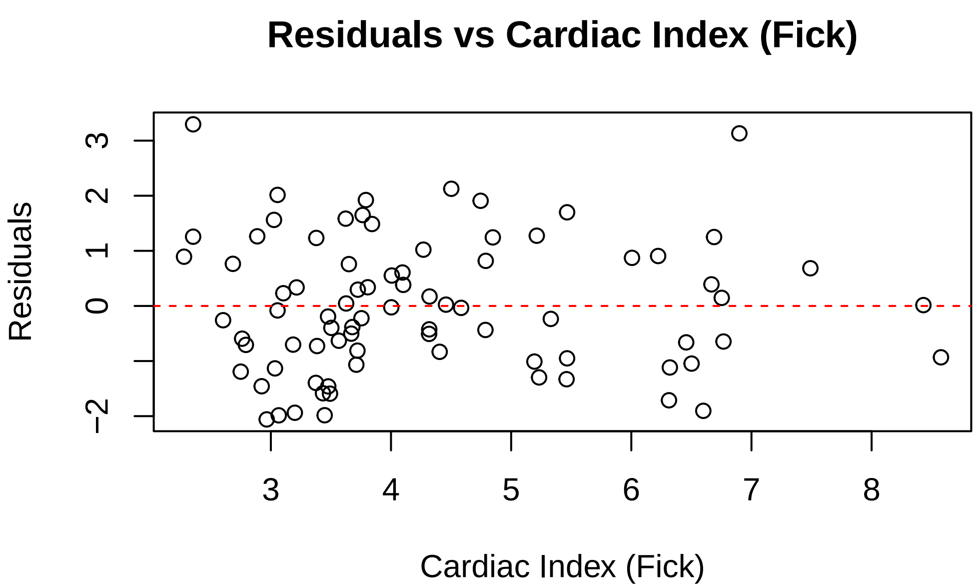
Non-linear relationship is not significantly better than linear relationship. Thus, I will model as linear relationship.

Pearson correlation

```
	Pearson's product-moment correlation

data:  data$cardiac_index_TTE and data$cardiac_index_Fick
t = -0.47421, df = 79, p-value = 0.6367
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 -0.2685034  0.1670148
sample estimates:
        cor
-0.05327754
```

Linear regression

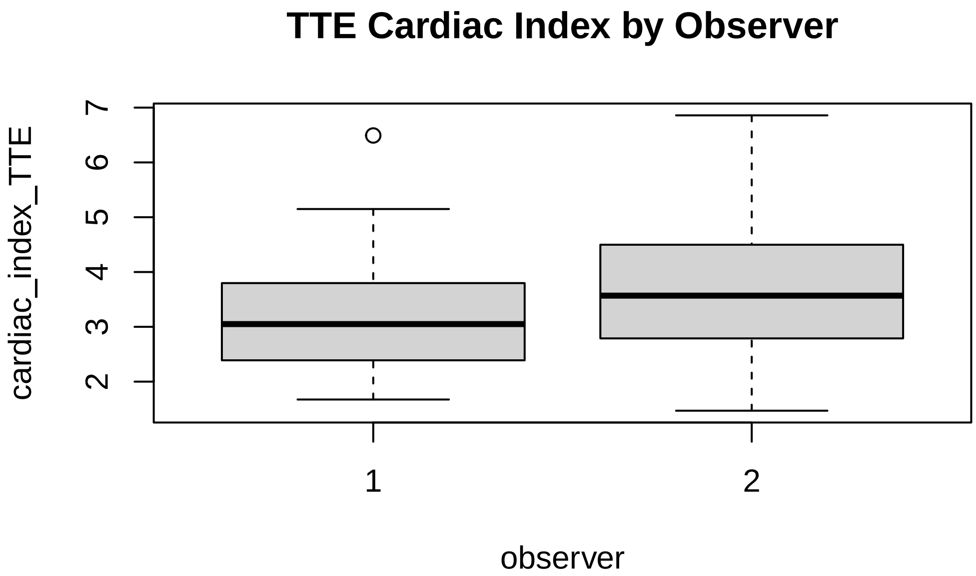
```
Call:
lm(formula = cardiac_index_TTE ~ cardiac_index_Fick, data = data)

Residuals:
    Min      1Q  Median      3Q     Max 
-2.0591 -0.9323 -0.0813  0.8727  3.2967 

Coefficients:
                   Estimate Std. Error t value Pr(>|t|)    
(Intercept)         3.66720    0.42949   8.539 7.75e-13 ***
cardiac_index_Fick -0.04462    0.09409  -0.474    0.637    
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.222 on 79 degrees of freedom
Multiple R-squared:  0.002838,  Adjusted R-squared:  -0.009784 
F-statistic: 0.2249 on 1 and 79 DF,  p-value: 0.6367
```



Linear Mixed Effects Model

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

REML criterion at convergence: 269.2

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.6281 -0.3603 -0.1032  0.2624  2.4707

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 1.4125   1.1885
 time_point (Intercept) 1.4002   1.1833
 Residual               0.4453   0.6673
Number of obs: 81, groups:  ID, 52; time_point, 9

Fixed effects:
                  Estimate Std. Error t value
(Intercept)        5.10906    0.66721   7.657
cardiac_index_TTE -0.02765    0.11350  -0.244

Correlation of Fixed Effects:
            (Intr)
crdc_nd_TTE -0.649
```

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



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

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

REML criterion at convergence: 267.3

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.60913 -0.37366 -0.09225  0.33037  2.41000

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 1.3645   1.1681
 time_point (Intercept) 1.4009   1.1836
 Residual               0.4492   0.6702
Number of obs: 81, groups:  ID, 52; time_point, 9

Fixed effects:
                  Estimate Std. Error t value
(Intercept)        5.40040    0.69415   7.780
cardiac_index_TTE -0.01631    0.11356  -0.144
observer2         -0.54588    0.37553  -1.454
```

```
Correlation of Fixed Effects:
            (Intr) c__TTE
crdc_nd_TTE -0.597
observer2   -0.281 -0.083

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

REML criterion at convergence: 268.9

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.6195 -0.3748 -0.1075  0.3062  2.4468

Random effects:
 Groups     Name        Variance Std.Dev.
 ID         (Intercept) 1.37062  1.1707
 time_point (Intercept) 1.40110  1.1837
 observer   (Intercept) 0.07816  0.2796
 Residual               0.44678  0.6684
Number of obs: 81, groups:  ID, 52; time_point, 9; observer, 2

Fixed effects:
                  Estimate Std. Error t value
(Intercept)        5.12133    0.69455   7.374
cardiac_index_TTE -0.02231    0.11326  -0.197

Correlation of Fixed Effects:
            (Intr)
crdc_nd_TTE -0.619

Data: data
Models:
linear_mixed_model: cardiac_index_Fick ~ cardiac_index_TTE + (1 | ID) + (1 | time_point)
linear_mixed_model_obs_fixed: cardiac_index_Fick ~ cardiac_index_TTE + observer + (1 | ID) +
                             npar    AIC    BIC  logLik -2*log(L)  Chisq Df
linear_mixed_model              5 277.16 289.13 -133.58    267.16
linear_mixed_model_obs_fixed    6 277.03 291.40 -132.52    265.03 2.1244  1
                             Pr(>Chisq)
```

```
linear_mixed_model
linear_mixed_model_obs_fixed      0.145
```

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_index_Fick ~ cardiac_index_TTE + (1 | ID) + (1 | time_point)
linear_mixed_model_obs_random: cardiac_index_Fick ~ cardiac_index_TTE + (1 | ID) + (1 | time_
                              npar    AIC    BIC  logLik -2*log(L)  Chisq Df
linear_mixed_model               5 277.16 289.13 -133.58    267.16
linear_mixed_model_obs_random    6 278.93 293.30 -133.47    266.93 0.2263  1
                              Pr(>Chisq)
linear_mixed_model
linear_mixed_model_obs_random     0.6343
```

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) = -0.044

F-Test, H0: r0 = 0 ; H1: r0 > 0
F(80,75.2) = 0.9 , p = 0.678

95%-Confidence Interval for ICC Population Values:
 -0.22 < ICC < 0.147
```

ID	CI 1 (TTE), L/min	CI 2 (TTE), L/min	CI 3 (TTE), L/min	Mean CI TTE, L/min	CV (%)	CE (%)	CI (Fick method), L/min
1	3.18	3.59	3.10	3.29	8.02	4.63	2.60
2	7.31	6.51	6.76	6.86	5.96	3.44	2.35
2	4.93	4.90	4.62	4.82	3.52	2.03	2.35
3	2.30	2.42	2.34	2.35	2.74	1.58	8.58
3	2.67	2.77	2.72	2.72	1.83	1.05	6.46
4	1.54	1.61	1.49	1.55	3.74	2.16	3.07

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: 33.52%

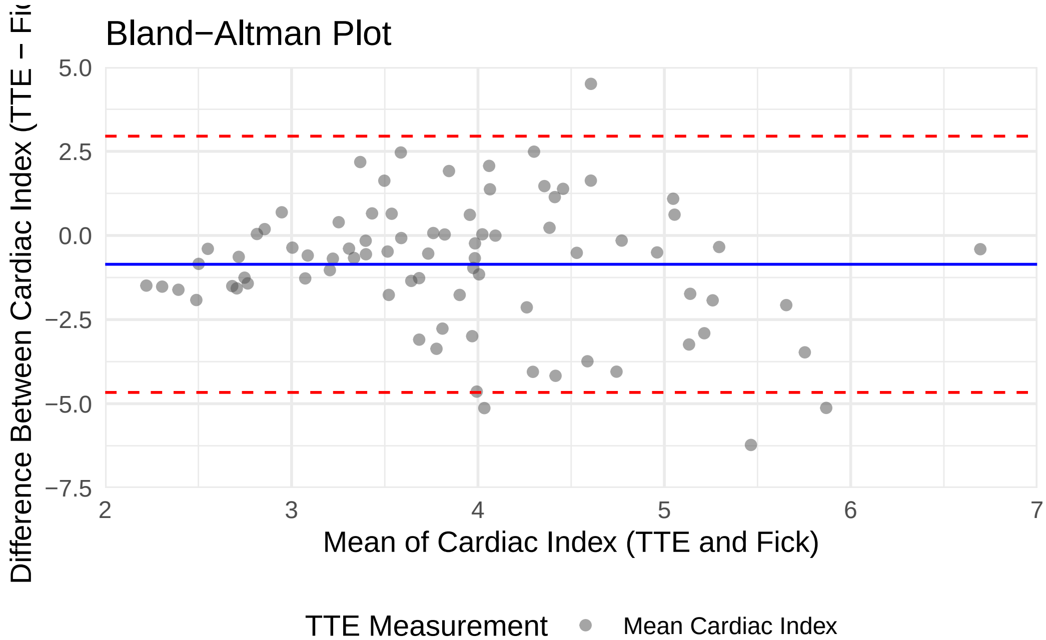
TTE CV: 35%

Because there are multiple measurements that are averaged to produce the mean cardiac index 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)

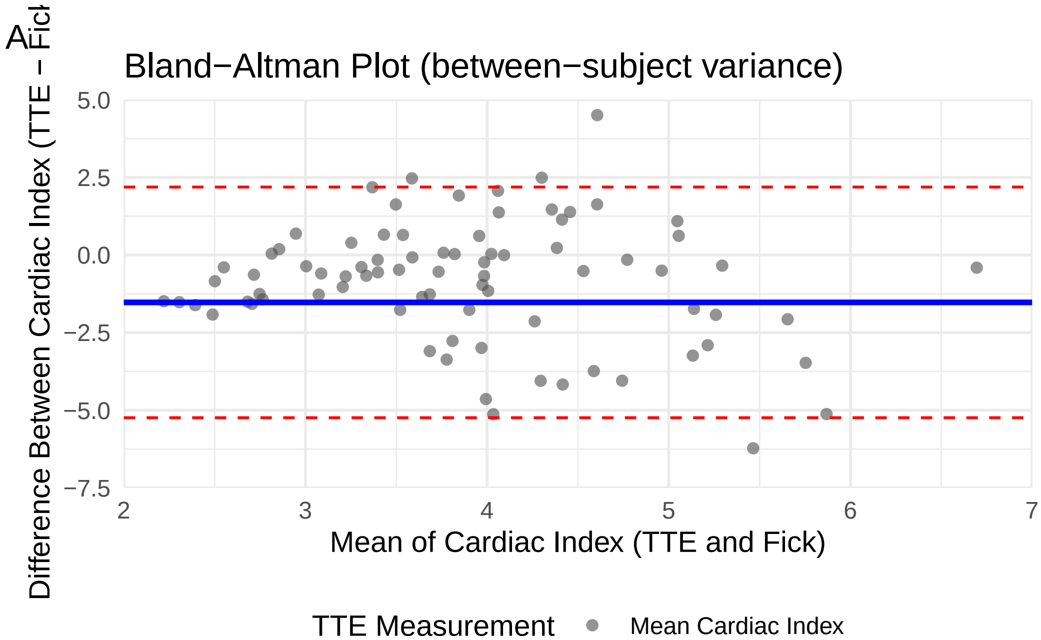
```
	Paired t-test

data:  data$cardiac_index_TTE and data$cardiac_index_Fick
t = -3.9695, df = 80, p-value = 0.0001563
alternative hypothesis: true mean difference is not equal to 0
95 percent confidence interval:
 -1.2863075 -0.4272454
sample estimates:
mean difference 
     -0.8567765 
```

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             3 324.50 331.68 -159.25    318.50
model_observer    4 323.63 333.21 -157.82    315.63 2.8677  1    0.09037 .
---
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: 316.1

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.22225 -0.41478  0.02696  0.33161  1.99381

Random effects:
 Groups   Name        Variance Std.Dev.
 ID       (Intercept) 2.136    1.461
 Residual             1.456    1.207
Number of obs: 81, groups:  ID, 52

Fixed effects:
            Estimate Std. Error t value
(Intercept)  -1.5257     0.4023  -3.793
observer2     0.8710     0.5151   1.691

Correlation of Fixed Effects:
          (Intr)
observer2 -0.781
```


A
Bland−Altman Plot (between−subject variance)
Difference Between Cardiac Index (TTE − Fick
5.0
2.5
0.0
−2.5
−5.0
−7.5
2
3
4
5
6
7
Mean of Cardiac Index (TTE and Fick)
TTE Measurement
Mean Cardiac Index

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

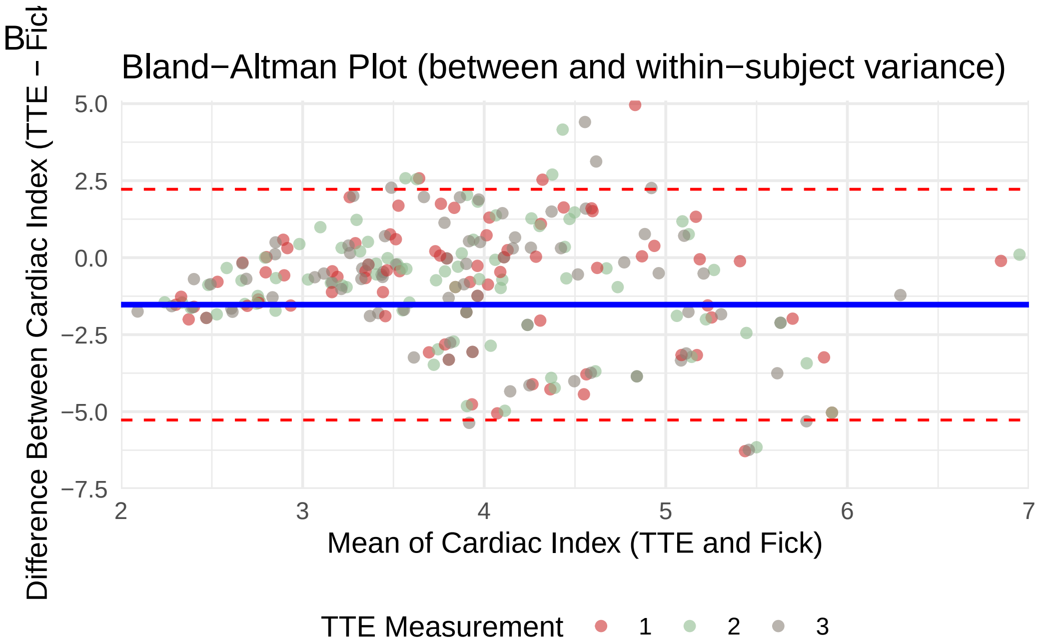
```
Data: data_long
Models:
model_long: differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement)
model_long_observer: differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement)
                    npar    AIC    BIC  logLik -2*log(L)  Chisq Df Pr(>Chisq)
model_long             5 485.44 502.91 -237.72    475.44
model_long_observer    6 484.58 505.54 -236.29    472.58 2.8677  1    0.09037 .
---
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. Thus, will include.

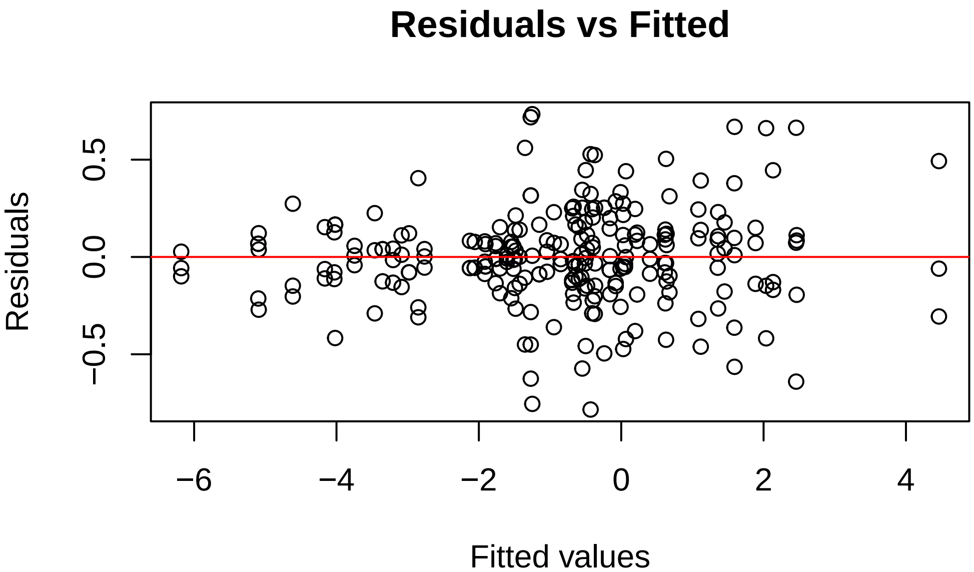
```
Linear mixed model fit by REML ['lmerMod']
Formula:
differences ~ 1 + (1 | ID) + (1 | ID:time_point) + (1 | TTE_measurement) +
    observer
   Data: data_long

REML criterion at convergence: 473

Scaled residuals:
     Min       1Q   Median       3Q      Max
-2.62688 -0.42775 -0.02655  0.40275  2.45866

Random effects:
 Groups          Name        Variance Std.Dev.
 ID:time_point   (Intercept) 1.42584  1.1941
 ID              (Intercept) 2.13629  1.4616
 TTE_measurement (Intercept) 0.00000  0.0000
 Residual                    0.08906  0.2984
Number of obs: 243, groups:  ID:time_point, 81; ID, 52; TTE_measurement, 3

Fixed effects:
            Estimate Std. Error t value
(Intercept)  -1.5257     0.4023  -3.793
observer2     0.8709     0.5152   1.691

Correlation of Fixed Effects:
```

```
           (Intr)
observer2 -0.781
optimizer (nloptwrap) convergence code: 0 (OK)
boundary (singular) fit: see help('isSingular')
```

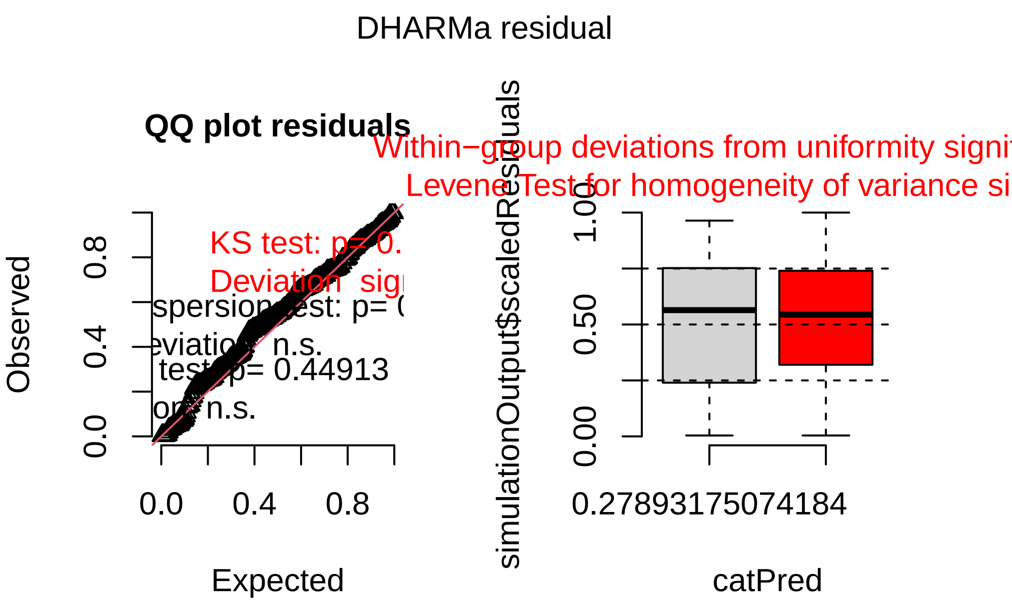
There was singularity in the prior model including a random effect for within-subject TTE measurements. Because this term is conceptually important to take into account the nested structure of the data, we will keep it in the model. Other alternatives would be to include it as a fixed effect, but this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



Residuals and random effects diagnostics



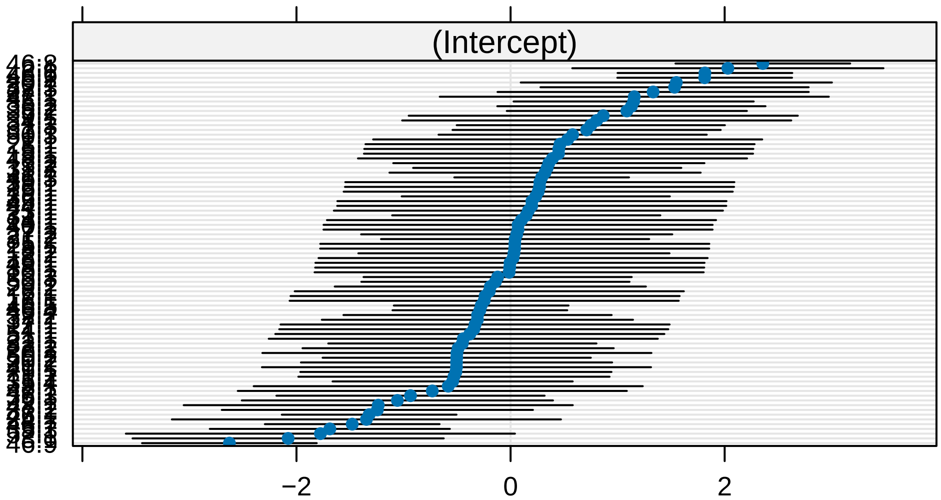
Overall, apparent random distribution of residuals.



Diagnostics form predicted residuals show random distribution, although no perfect match with a normal distribution. There is no heteroskedasticity. Relationship likely linear. No evidence of influential outliers. Including observer fixed effect further improved fit and random distribution of residuals. Although not perfect, residuals analysis plus the prior analyses with cardiac output would together suggest that the model is appropriate, although there could possibly be improvements for cardiac index model.

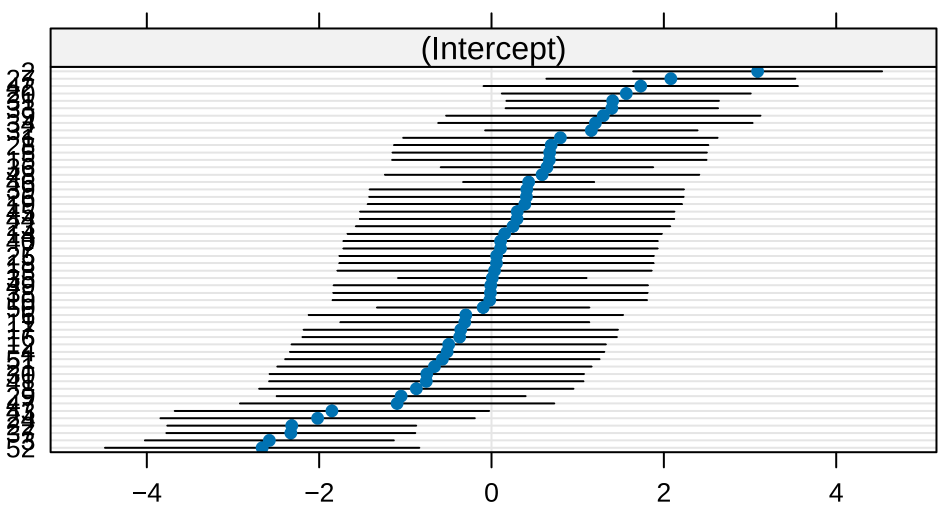
$`ID:time_point`

ID:time_point

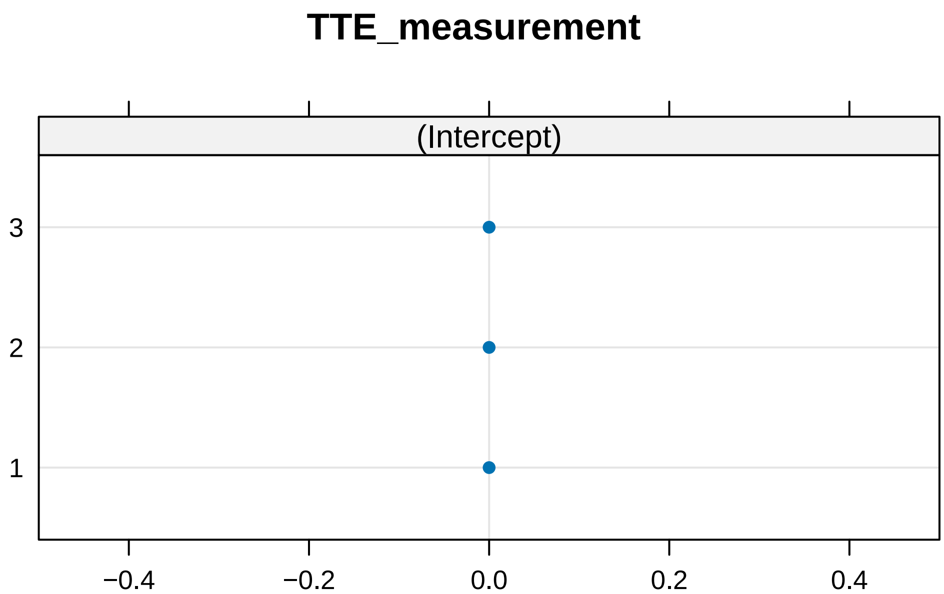


$ID

ID



$TTE_measurement



Symmetric 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 index is 1.6 (95% CI: 1.2 to 2).

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 index with TTE was 3.47 (95% CI: 3.21 to 3.74) L/min, and 4.33 L/min (95% CI: 4.04 to 4.67) for the Fick method. The correlation between the two methods was rho = -0.05 (95% CI: -0.27 to 0.17, p=0.637). In a linear mixed model with random patient slopes, there was a change in Fick CI of -0.016 (95% CI: -0.247 to 0.206) L/min for each unit change in mean TTE CI. The ICC between TCE and Fick CI -0.04 (95% CI: -0.22 to 0.15).

The mean absolute difference in CI between TTE and Fick was 1.59 (95% CI: 1.2 to 2) L/min. The coefficient of variation for an individual measurement of TTE was 35% and 33.52% 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 2 shows the Bland-Altman plot for the repeated measures model with random effects for between-subject variance (Figure2A) and within-subject variance (Figure2B). The mean difference (systematic bias) between TTE and Fick CI was -1.53 (95% CI: -2.31 to -0.74, p = 0) L/min, with 95% limits of agreement of -5.27 to 2.22 L/min.

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