Validation of Fick cardiac output calculated with assumed oxygen consumption: a study of cardiac output during epoprostenol administration

A. Bergstra, A.F.M. van den Heuvel, F. Zijlstra, R.M.F. Berger, G.A. Mook, D.J. van Veldhuisen

Objective. To test the validity of using assumed oxygen consumption for Fick cardiac output during administration of epoprostenol.
Methods. In 24 consecutive patients Fick cardiac output calculated with assumed oxygen consumption according to LaFarge and Miettinen (COLM) and according to Bergstra et al. (COBE) were compared with thermodilution cardiac output (COTH). Pulmonary vascular resistance (PVR) was calculated with each cardiac output (CO) value. If PVR exceeded 200 dyne.s.cm^{-5}, administration of epoprostenol (Ep) was started, and at maximal dose the above-mentioned measurements were repeated.
Results. In all 24 patients COBE agreed significantly with COTH, mean difference -0.145 l.min^{-1}, 95% confidence interval (CI) -0.402 to 0.111, limits of agreement (LA) -1.336 to 1.045. COLM was significantly lower than COTH, -1.165 l.min^{-1}, p<0.05, 95% CI -1.510 to -0.819, LA -2.768 to 0.438. In 16 patients (67%) administration of epoprostenol was indicated. During Ep infusion the CO values calculated with oxygen consumption according to LaFarge and Miettinen (EpCOLM) were also significantly lower than thermodilution CO (EpCOTH), mean difference -1.281 l.min^{-1}, p<0.05, 95% CI -1.663 to -0.900, LA -2.685 to 0.122. The agreement of CO values calculated with oxygen consumption according to Bergstra et al. (EpCOBE) and EpCOTH remained, mean difference -0.115 l.min^{-1}, 95% CI -0.408 to 0.178, LA -1.191 to 0.962.
Conclusion. Before as well as during administration of epoprostenol, it is justified to use CO values calculated with oxygen consumption according to Bergstra et al. instead of thermodilution CO; CO values calculated with oxygen consumption according to LaFarge and Miettinen show significant underestimation. (*Neth Heart J* 2004;12:208-13.)

Key words: cardiac output, epoprostenol, oxygen consumption, pulmonary hypertension, pulmonary vascular resistance, thermodilution

In patients with pulmonary hypertension accurate information about reactivity of the pulmonary vascular system is essential, since fixed pulmonary hypertension may be a contraindication for several operative interventions. One of the methods to test the reactivity is the determination of pulmonary vascular resistance (PVR) before and during infusion of an increasing dose of epoprostenol.[1] In addition to accurate pulmonary artery and pulmonary wedge pressures, accurate cardiac output (CO) values are necessary. A fast, but rough, estimation of the CO can be made by means of a central venous oxygen saturation and haemoglobin concentration; low oxygen saturation with a normal haemoglobin concentration indicates a low CO. The direct Fick method and the dye dilution method have been the methods of choice for a long time. Since the introduction of the Swan-Ganz catheter in 1970 the thermodilution method is most frequently applied in spite of some sources of error and the unsuitability in cases of intracardiac shunts. One condition for CO determination according to the indicator dilution method, namely no loss of indicator between injection

A. Bergstra
A.F.M. van den Heuvel
F. Zijlstra
D.J. van Veldhuisen
Department of Cardiology, Thorax Centre, University Hospital Groningen, PO Box 30001, 9700 RB Groningen
R.M.F. Berger
Division of Paediatric Cardiology of the Beatrix Children's Hospital, University Hospital Groningen
G.A. Mook
Emeritus of the Department of Medical Physiology, University of Groningen

Correspondence to: A. Bergstra
E-mail: a.bergstra@thorax.azg.nl

and detection site, is not fulfilled using cold as indicator. Most systems apply a factor 0.7 to 0.8 to correct for the 20 to 30% loss of indicator. The equation used to calculate the CO only holds for constant flow. Due to respiration the flow is not constant. In practice this does not appear to be a serious problem, provided the CO is calculated as the average of at least three consecutive measurements evenly spread within the respiratory cycle.[2] According to another study,[3] the average of the results of four to seven standardised injections should be used. Because of this, application of the thermodilution method, with the inherent volume load, may be contraindicated in seriously ill patients. Moreover, the application requires a lot of discipline and time from the nursing staff. Estimated oxygen consumption for Fick CO is used in routine clinical practice in the care of patients admitted to the catheterisation laboratory,[4] coronary care unit, intensive care unit and operating room. In a previous study, the agreement of Fick CO calculated with assumed oxygen consumption according to Bergstra et al. and dye dilution CO was shown.[5] However, justification of using assumed oxygen consumption in other than basic conditions should be demonstrated. In this study the thermodilution CO (COTH) was compared with CO values obtained using assumed oxygen consumption according to LaFarge and Miettinen (COLM) and according to Bergstra et al. (COBE),[5,6] before and during infusion of epoprostenol. To prevent volume load, thermodilution was only applied during control conditions and at a maximal dose of epoprostenol. The aim of the study was to evaluate the use of Fick CO based on assumed oxygen consumption before and during epoprostenol infusion.

Materials and methods

Patients

The study was performed in the Department of Cardiology Thorax Centre of the University Hospital of Groningen in 24 consecutive patients (15 male, 9 female) thought to have pulmonary hypertension, who were submitted for cardiac catheterisation to evaluate whether their pulmonary vascular system would show reactivity on administration of epoprostenol (Flolan; GlaxoSmithKline; US). Five patients (21%) had atrial fibrillation and two (8%) had a ventricular pacemaker. Three patients (13%) were candidates for liver transplantation, eleven (46%) for heart transplantation, two (8%) for lung transplantation and eight (33%) patients had valvular disease. Patients' characteristics are shown in table 1.

Catheterisation procedure

Prior to the catheterisation procedure, body height (m) and body mass (kg) were measured and the body surface area (BSA m^2) was calculated according to DuBois and DuBois.[7] Right heart catheterisation was

Table 1. Patient characteristics (n=24).

	Mean±SD	Range
Age (years)	55.5±13.1	20-82
Height (m)	1.73 ±0.09	1.57-1.89
Weight (kg)	81.9±20.0	55.0-147.0
BSA (m^2)	1.95±0.24	1.58-2.60

Table 2. Haemodynamic data (n=24).

	Mean±SD	Range
SaO_2 (%)	93.6±5.3	79.8-100.0
$SpaO_2$ (%)	59.6±9.6	35.9-72.6
HR (min^{-1})	77.9±15.7	44-120
COBE ($l.min^{-1}$)	5.19±1.75	2.13-8.70
COLM ($l.min^{-1}$)	4.17±1.46	1.82-6.95
COTH ($l.min^{-1}$)	5.33±1.98	2.10-10.10
PVRBE ($dyne.s.cm^{-5}$)	332±186	129-976
PVRLM ($dyne.s.cm^{-5}$)	408±204	163-1083
PVRTH ($dyne.s.cm^{-5}$)	330±191	104-990

SaO_2=oxygen saturation of arterial blood, $SpaO_2$=oxygen saturation of pulmonary arterial blood, HR=heart rate, COBE=cardiac output according to Bergstra et al., COLM=cardiac output according to Lafarge and Miettinen, COTH=cardiac output measured by the thermodilution method, PVRBE= pulmonary vascular resistance calculated with COBE, PVRLM=pulmonary vascular resistance calculated with COLM, PVRTH=pulmonary vascular resistance calculated with COTH.

Table 3. Haemodynamic data during epoprostenol infusion (n=16).

	Mean±SD	Range
SaO_2 (%)	92.6±5.8	78.3-100.0
$SpaO_2$ (%)	65.7±7.1	50.1-75.3
HR (min^{-1})	84.0±16.5	58-122
EpCOBE ($l.min^{-1}$)	6.29±1.61	3.28-8.53
EpCOLM ($l.min^{-1}$)	5.12±1.38	2.72-6.99
EpCOTH ($l.min^{-1}$)	6.40±1.85	3.37-9.18
EpPVRBE ($dyne.s.cm^{-5}$)	246±153	101-538
EpPVRLM ($dyne.s.cm^{-5}$)	302±185	112-706
EpPVRTH ($dyne.s.cm^{-5}$)	246±157	96-570

SaO_2=oxygen saturation of arterial blood, $SpaO_2$=oxygen saturation of pulmonary arterial blood, HR=heart rate, EpCOBE=cardiac output according to Bergstra et al. during epoprostenol, EpCOLM=cardiac output according to Lafarge and Miettinen during epoprostenol, EpCOTH=cardiac output measured by the thermodilution method during epoprostenol, EpPVRBE= pulmonary vascular resistance calculated with EpCOBE, EpPVRLM=pulmonary vascular resistance calculated with EpCOLM, EpPVRTH=pulmonary vascular resistance calculated with EpCOTH.

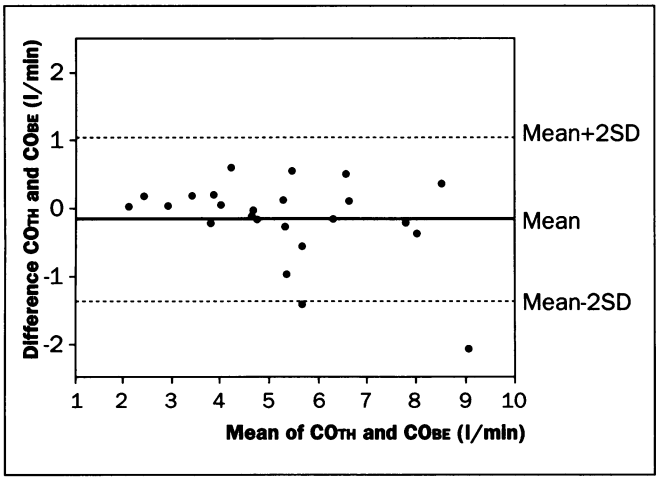

Figure 1A. Plot of mean and differences of thermodilution cardiac output (COTH) and cardiac output calculated with assumed oxygen consumption according to Bergstra (COBE). The mean difference and twice its standard deviation are shown.

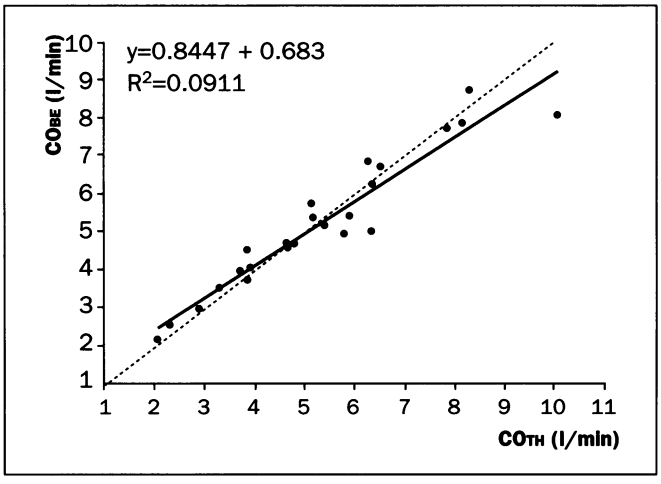

Figure 1B. Plot of thermodilution cardiac output (COTH) and cardiac output calculated with assumed oxygen consumption according to Bergstra (COBE). The solid line represents the regression line (n=24), the dashed line represents the line of identity.

performed using a Swan-Ganz thermodilution catheter (Edwards Lifesciences, Irvine, US), and pressures were measured in the right atrium, right ventricle, pulmonary artery and pulmonary artery wedge position successively. Thereafter, blood samples were taken from the pulmonary artery and from a femoral artery for determination of the oxygen saturation and haemoglobin concentration. Immediately after blood sampling, COTH was measured. If PVR calculated with COTH exceeded 200 dyne.s.cm^{-5}, the procedure was continued by intravenous infusion of epoprostenol. Starting dose was 2 ng.kg^{-1}.min^{-1} and was increased every five minutes by 2 ng.kg^{-1}.min^{-1} until the maximum dose of 12 ng.kg^{-1}.min^{-1} was reached. At the end of each five-minute period, pulmonary artery pressure and pulmonary wedge pressure were recorded. If either adverse reactions or a tendency to haemodynamic deterioration showed up, the present dose was considered as maximal, and blood sampling, pulmonary artery pressure, pulmonary capillary wedge pressure and COTH measurement were performed. Otherwise these measurements were performed at maximum epoprostenol dose. Then the remaining part of the catheterisation procedure was finished.

Methods

Oxygen saturation as well as the total haemoglobin concentration were measured with an AVOXimeter (A-Vox systems, Texas, US). Thermodilution cardiac output measurement was carried out by injection of 10 ml of 5% glucose solution at room temperature into the inferior caval vein or the right atrium. A cardiac output monitor (Vigilance, Edwards Lifesciences Irvine, US), in bolus injection mode, calculated cardiac output. The average of five to seven determinations was taken as definite cardiac output value.[3] The formulas for calculation of the oxygen consumption according to Bergstra et al. and LaFarge and Miettinen are presented in the appendix.[5,6] Heart rate (min^{-1}) was read during cardiac output determination.

Statistics

Values were given as mean±SD. The data of the three CO measurements (COTH, COBE, COLM) where compared by a two-way ANOVA with a Bonferroni correction. The Spearman rank-order correlation coefficient was used to investigate the associations between study parameters. To confirm that the data were normally distributed, the Shapiro-Wilk test was used. The agreement between the methods was assessed according to the Bland and Altman method.[8] A p value <0.05 was considered statistically significant. Statistical analysis was performed with SAS statistical software, version 11.0.

Results

In all 24 patients COBE agreed significantly with COTH, mean difference -0.145 l.min^{-1}, 95% confidence level (CI) -0.402 to 0.111, limits of agreement (LA) -1.336 to 1.045. COLM was significantly lower than COTH: -1.165 l.min^{-1}, $p<0.05$, 95% CI -1.510 to -0.819, LA -2.768 to 0.438. The distribution of the differences are shown in figures 1A and 2A, where the difference between COBE and COLM, respectively, and COTH are plotted against the mean of COBE and COLM, respectively, and COTH. Figures 1B and 2B present the correlation between the COBE and COLM, respectively, and COTH. Pulmonary vascular resistance (PVR, dyne.s.cm^{-5}) calculated with COBE was 332±186 vs. 330±191 calculated with COTH vs. 408±204 calculated with COLM. (COLM vs. COBE and COTH $p<0.05$).

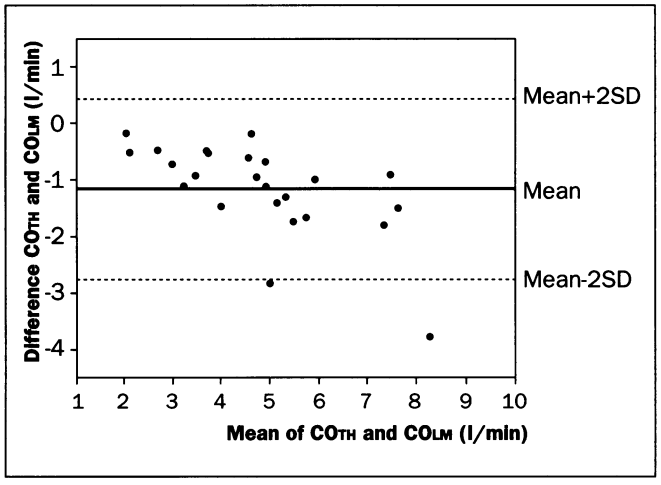

Figure 2A. Plot of mean and differences of thermodilution cardiac output (COTH) and cardiac output calculated with estimated oxygen consumption according to Lafarge and Miettinen (COLM). The mean difference and twice its standard deviation are shown.

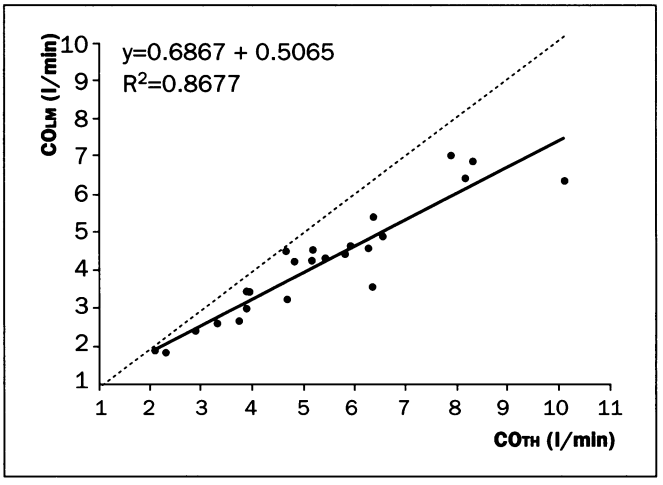

Figure 2B. Plot of thermodilution cardiac output (COTH) and cardiac output calculated with estimated oxygen consumption according to Lafarge and Miettinen (COLM). The solid line represents the regression line (n=24), the dashed line represents the line of identity.

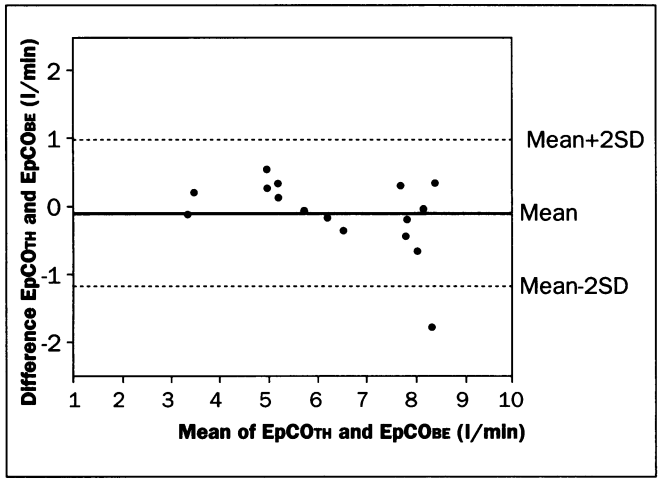

Figure 3A. Plot of mean and differences of thermodilution cardiac output (EpCOTH) and cardiac output calculated with assumed oxygen consumption according to Bergstra (EpCOBE) during administration of epoprostenol. The mean difference and twice its standard deviation are shown.

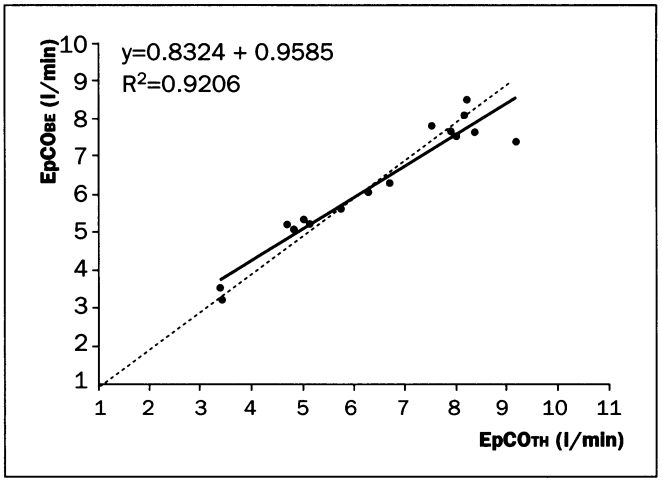

Figure 3B. Plot of thermodilution cardiac output (EpCOTH) and cardiac output calculated with assumed oxygen consumption according to Bergstra (EpCOBE) during administration of epoprostenol. The solid line represents the regression line (n=16), the dashed line represents the line of identity.

Sixteen patients (9 male, 7 female) had a PVR >200 dyne.s.cm^{-5}, calculated with COTH, and received epoprostenol infusion. With the COBE method the same 16 patients had a PVR >200 dyne.s.cm^{-5}, but calculated with COLM three more patients had a PVR >200 dyne.s.cm^{-5}. During epoprostenol (Ep) infusion EpCOLM values were also significantly lower than EpCOTH, mean difference -1.281 l.min^{-1}, p<0.05, 95% CI -1.663 to -0.900, LA -2.685 to 0.122. The agreement of EpCOBE and EpCOTH remained, mean difference -0.115 l.min^{-1}, 95% CI -0.408 to 0.178, LA -1.191 to 0.962. PVR calculated with EpCOBE was 246±154 vs. 246±158 calculated with EpCOTH vs. 303±185 calculated with EpCOLM (EpCOLM vs. EpCOBE and EpCOTH p<0.05). The distribution of the differences is shown in figures 3A and 4B and the correlations in figures 3B and 4B. Both in the EpCOTH and EpCOBE group the same six patients had a PVR >200 dynes.s.cm^{-5}, in the EpCOLM group three more patients still had a PVR >200 dynes.s.cm^{-5}.

Discussion

This study was performed to investigate whether the use of assumed oxygen consumption for the calculation of cardiac output during administration of epoprostenol is justified. In a recent study by Opitz et al.[9] estimated

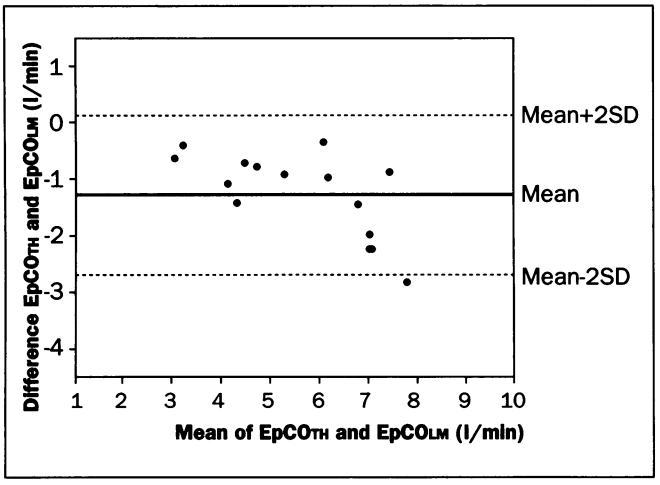

Figure 4A. Plot of mean and differences of thermodilution cardiac output (EpCOTH) and cardiac output calculated with estimated oxygen consumption according to Lafarge and Miettinen (EpCOLM) during administration of epoprostenol. The mean difference and twice its standard deviation are shown.

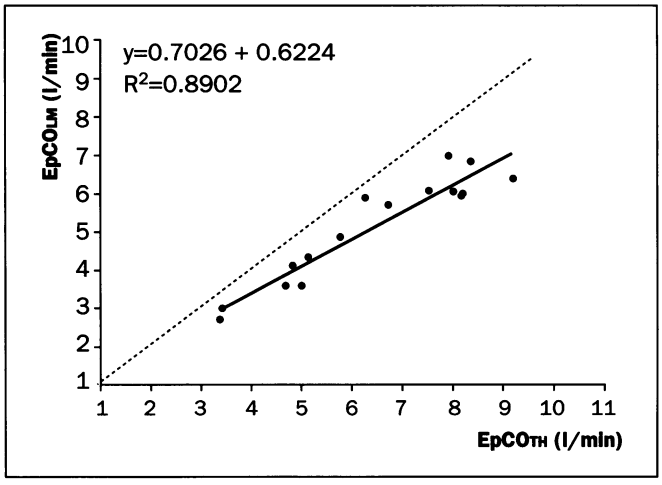

Figure 4B. Plot of thermodilution cardiac output (EpCOTH) and cardiac output calculated with estimated oxygen consumption according to Lafarge and Miettinen (EpCOLM) during administration of epoprostenol. The solid line represents the regression line (n=16), the dashed line represents the line of identity.

oxygen consumption was used in patients with primary pulmonary hypertension during at least three different conditions. They presumed that their interventions would not affect the patient's oxygen consumption. However, they neither referred to nor mentioned the method of calculation of oxygen consumption, which makes it difficult to compare their data with data from other studies. Our finding, that oxygen consumption does not significantly change by the administration of epoprostenol, is in agreement with the finding of Chappell et al.[10] They measured oxygen consumption and thermodilution cardiac output in 22 of their 35 patients. Their measured oxygen consumption and oxygen consumption calculated with the thermodilution cardiac output according to Fick were not significantly different. Moreover, despite significant increases in cardiac output during administration of vasodilators, oxygen consumption did not change significantly. The difference between estimated oxygen consumption according to LaFarge and Miettinen and according to Bergstra et al. has been published previously.[5,6] This difference is probably caused by an imbalance in the age distribution of the LaFarge and Miettinen patient population.

Conclusions

From the present study it can be concluded that Fick cardiac output, calculated with assumed oxygen consumption according to Bergstra et al. agrees well with thermodilution cardiac output,[5] even during administration of epoprostenol. Besides, cardiac output monitoring during a longer period can easily be performed by intermittent or continuous measurement of arterial and mixed venous oxygen saturation,[11] that may prevent volume load by multiple application of thermodilution.

Clinical implications

If the administration of epoprostenol had been decided on PVR calculated with cardiac output based on the Lafarge and Miettinen formulas,[6] three patients would have received epoprostenol unnecessarily. Moreover, three other patients might have been rejected for heart transplantation, for example, because of a persistent PVR >200 dynes.s.cm^{-5} during epoprostenol administration. ■

Acknowledgement

We thank Nic Veeger, from the statistical department of the Trial Coordination Centre, University Hospital, Groningen for his statistical advice.

Appendix

Oxygen consumption according to Bergstra et al.:
VO_2BE = (157.3 x BSA + 10.0 x Sex - 10.5 x ln Age + 4.8) ml.min^{-1},
Oxygen consumption according to LaFarge and Miettinen:
for male: VO_2LM = (138.1 – 11.49 x in Age + 0.378 x HR) x BSA ml.min^{-1}, for female: VO_2LM = (138.1 – 17.04 x ln Age + 0.378 x HR) x BSA ml.min^{-1}, where BSA=body surface area (m^2) ln Age=the natural logarithm of the age (yr), Sex=1 for male and 0 for female, HR=heart rate (min^{-1}).

Fick cardiac output (CO) was calculated as follows:
$CO=VO_2$ x 100 / ((SaO_2 - $SpaO_2$) x cHb x 1.36) l.min^{-1}, where SaO_2=arterial oxygen saturation (%), $SpaO_2$=pulmonary arterial oxygen saturation (%), cHb=hemoglobin concentration (g.l^{-1}), 1.36=oxygen binding capacity of hemoglobin (ml.g^{-1}) and 100=conversion factor.

References

1 Robbins IM, Christman BW, Newman JH, Matlock R, Loyd JE. A survey of diagnostic practices and the use of epoprostenol in patients with primary pulmonary hypertension. *Chest* 1998;**114**: 1269-75.

2 Delhaas T, Mook GA, Zijlstra WG. Respiration and measurement of cardiac output by thermodilution and central or peripheral dye dilution. *J Appl Physiol* 1992;**73**:1047-51.

3 Bourdillon PDV, Fineberg N. Comparison of iced and room temperature injectate for thermodilution cardiac output. *Cathet Cardiovasc Diagn* 1989;**17**:116-20.

4 Kendrick AH, West J, Papouchado M, Rozkovec A. Direct Fick cardiac output: Are assumed values of oxygen consumption acceptable? *Eur Heart J* 1988;**9**:337-42.

5 Bergstra A, Dijk RB van, Hillege HL, Lie KI, Mook GA. Assumed oxygen consumption based on calculation from dye dilution cardiac output: an improved formula. *Eur Heart J* 1995;**16**:698-703.

6 LaFarge CG, Miettinen OS. The estimation of oxygen consumption. *Cardiovasc Res* 1970;**4**:23-30.

7 Du Bois D, Du Bois EF. Clinical calorimetry. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;17:863-71.

8 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307-10.

9 Opitz CF, Wensel R, Bettmann M, Schaffarczyk R, Linscheid M, Hetzer R, et al. Assessment of the vasodilator response in primary pulmonary hypertension. *Eur Heart J* 2003;**24**:356-65.

10 Chappell TR, Rubin LJ, Markham RV Jr, Firth BG. Independence of oxygen consumption and systemic oxygen transport in patients with either stable pulmonary hypertension or refractory left ventricular failure. *Am Rev Respir Dis* 1983;**128**:30-3.

11 Bergstra A, Dijk RB van, Brekke O, Buurma AE, Orozco L, Den Heijer P, et al. Hemodynamic effects of iodixanol and iohexol during ventriculography in patients with compromised left ventricular function. *Cathet Cardiovasc Interv* 2000;**50**:314-21.