Chapter 3.

Meta-regression analysis of High Frequency Ventilation versus Conventional Ventilation in Infant Respiratory Distress Syndrome

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Submitted

ABSTRACT

Objective

Meta-analyses have been conducted of randomized trials to determine whether high frequency ventilation (HFV) in premature neonates with respiratory distress syndrome resulted in favourable pulmonary outcome compared with conventional mechanical ventilation (CMV). Considerable heterogeneity was detected. Hypotheses have been formulated to explain differences in outcome between these trials.

Design

Meta-regression analysis was used to evaluate these hypotheses.

Measurements and results

Variables were extracted to explain heterogeneity: year of publication, use of SensorMedics 3100A ventilator for HFV, time on CMV prior to start of study, gestational age, use of surfactant, high lung volume strategy in HFV, lung protective ventilation strategy in CMV and baseline risk. Chronic lung disease (CLD) and death or CLD were outcome measures. Relative risk rates were calculated to estimate effect sizes of explanatory variables on reported relative risks. Adjusted estimates of relative risk rates of use of high lung volume strategy and lung protective ventilation strategy were 0.42 (95% CI 0.06-2.48) and 2.02 (95% CI 0.18-23.12) for CLD, respectively. The effect of gestational age was less pronounced (RRR = 1.17 (95% CI 0.16-8.32) for CLD, respectively). Use of SensorMedics and prior time on CMV had the smallest effects (RRR = 0.96 (95% CI 0.47-1.94) and RRR = 0.85 (95% CI 0.58-1.24) for CLD, respectively). The same results applied to CLD or death as outcome.

Conclusions

Differences between trials comparing HFV with CMV on pulmonary outcome in premature neonates with respiratory distress syndrome could be largely explained by differences in ventilation strategies adjusted by other explanatory variables.

Introduction

High frequency ventilation (HFV) has been compared with conventional mechanical ventilation (CMV) since the 1980s. In HFV, patients are ventilated with small tidal volumes, even smaller than the dead space of their airways, at high frequencies, normally between five and ten Hz. Because HFV combines high mean airway pressures with small tidal volumes, this technique of ventilation has been regarded by some to be the most optimal form in patients with infant respiratory distress syndrome (IRDS), adult respiratory distress syndrome (ARDS), and other forms of severe lung disease [1].

HFV has been extensively investigated in premature neonates with IRDS, a population very susceptible for chronic lung disease (CLD). Unfortunately, the results of these studies were equivocal. Thus, the question remains whether or not HFV is able to prevent CLD as compared with conventional mechanical ventilation (CMV) in patients with severe lung disease. A significant number of meta-analyses have been performed to answer this question [2-6]. Pooled estimates of pulmonary outcomes failed to show clinically relevant differences between HFV and CMV [5]. However, significant heterogeneity existed between studies included in these meta-analyses. In a recent cumulative meta-analysis, we identified improvements of the conventional treatment of IRDS and ventilation strategies applied in both HFV and CMV as important sources of heterogeneity [2]. These associations could be confounded by other explanatory variables. Although a meta-analysis may pool results from randomized trials, differences between trials will not be randomly or independently distributed. A meta-analysis constitutes an observational study of trials, subjected to bias inherent to observational research. In a meta-regression analysis it is possible to adjust for confounding covariates.

A number of alternative hypotheses have been formulated to explain heterogeneity between trials [7;8]. Therefore, meta-regression analysis was used to obtain less biased estimates of the effects of explanatory variables on relative treatment effect by adjusting by other covariates.

Methods

Trials were included based on a previous meta-analysis that we conducted [2]. An additional literature search yielded two more studies that could be included for this meta-regression analysis. The same inclusion and exclusion criteria were used. Validity of studies was assessed by criteria published by Jadad et al. [9]. The validity was generally deemed as high with adequate allocation concealment in all trials. Blinding of treatment was not possible due to the nature of the interventions.

Data extraction was performed as has been reported in our previous meta-analysis. The following outcome measures were used: mortality, chronic lung disease (CLD) as defined by supplemental oxygen need or ventilator dependency at the age of 30-36 weeks post-menstrual. A number of explanatory variables were extracted as well: year of publication, type of ventilator used for HFV (SensorMedics 3100A ventilator versus other), ventilation strategies applied in the HFV and CMV treatment groups were obtained as previously described [2], time on CMV before study initiation, gestational age and birth weight and outcome rates in the control population were taken as proxy for baseline disease severity in the source population.

In a cumulative meta-analysis we showed that improvements in management of IRDS, i.e. introduction of surfactant and employment of lung protective strategies in CMV was associated with a diminishing

relative benefit of HFV on pulmonary outcome independent of whether or not a high lung volume strategy was used in HFV [2]. A number of competing hypotheses could bias this association: (1) the observed regression of the cumulative relative risks to the level of unity was due to publication bias, (2) use of the SensorMedics ventilator resulted in better results in HFV treated patients, (3) a prolonged ventilation on CMV before initiating HFV treatment could reduce the benefits of HFV, (4) in subgroups of more premature neonates, i.e. with lower birth weight with a higher susceptibility for CLD, HFV could result in better pulmonary outcome, and (5) with increasing outcome rates representing increasing disease severity HFV could have an increasing advantage over CMV.

Statistical analysis

All data were extracted according to the intention-to-treat principle. The number of patients surviving without chronic lung disease was subtracted from the total number of randomized patients in each treatment arm to calculate the composite outcome of death or chronic lung disease. To calculate the risk of chronic lung disease, the number of surviving patients was put in the denominator. Publication bias was assessed by funnel plots. A stratified analysis by ventilation strategies of publication bias was performed to determine whether the observed association between the inverse of the standard error with the risk ratio was confounded by ventilation strategies (Figure 6). Meta-regression analysis was used to evaluate other hypotheses. First, univariate linear regression analyses were applied to explanatory variables using the natural logarithm of relative risks for CLD and death or CLD as dependent variables. Individual studies were weighted by inverse variances of relative risks of outcomes of interest. Secondly, univariate linear regression analyses with continuous covariates were conducted stratified by HLVS, LPVS and use of surfactant. Finally, multivariate linear regression analyses were performed to calculate adjusted contributions of different explanatory variables of

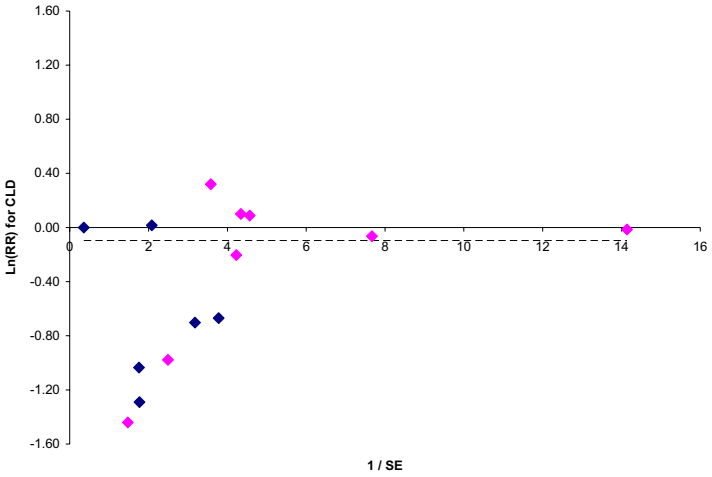
rivalling hypotheses to changes in RR. The relative effects of covariates were evaluated by relative risk ratios (RRR). For continuous variables the RRR was calculated for the extremes of these variables that were reported in trials. All analyses were conducted using SPSS 12.0.1 for Windows software (SPSS Inc., Chicago, Illinois, U.S.).

Results

For the analyses 15 studies were available that specified either CLD in survivors or death or CLD as outcome measures [10-24]. In the HFV group a total of 1141 patients were included for the outcome of CLD with 373 events and a total of 1457 patients with 671 events for the outcome death or CLD. In the CMV group a total of 1159 patients were reported for the outcome of CLD with 428 events and a total of 1473 patients with 730 events for the outcome death or CLD.

Table 1 summarizes the main characteristics of the studies. The outcome of CLD was available in all studies but one [22]. Time on CMV to start of the study was not reported by Plavka et al. and Craft et al. [15;21]. In only one study surfactant was not used as concomitant treatment [10]. A high lung volume strategy (HLVS) was used in all but two studies [12;14]. A ventilation strategy in the CMV treated patients that could qualify as lung protective (LPVS) was reported in the most recent 9 studies [16-24]. Studies were published over a range of 13 years. Other reported ranges of covariates were 8.7 hours, 5 weeks, 0.65 kg for average time on CMV before start of study, average gestational age, and average birth weight, respectively. These ranges were used to calculated relative risk rates. Two studies dominated the analyses by virtue of the weight they received in the analyses, Johnson et al. and Courtney et al. (together 69% for CLD and 73% for death or CLD as outcome) [19;20].

Figure 1. Funnel plot



Selection bias in reporting RR of CLD as suggested by asymmetry of the distribution of studies. X-axis: Inverse of the standard error of the RR. Y-axis: natural logarithm of the RR. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Dotted line;: estimated RR including all studies.

A funnel plot of inverse of the standard error versus the natural logarithm of risk ratio for CLD was indicative of publication bias with a rank test p-value of 0.112 (Figure 1). Stratification by ventilation strategy (HLVS and LPVS versus either no HLVS and/or no LPVS) showed p-values of 0.456 and 0.851, respectively. Publication bias for the composite outcome of death or CLD was less likely with a p-value of 0.329. Stratified analysis showed p-values of 0.677 and 1.000.

Figures 2 to 4 show the results of the univariate linear meta-regression analyses for continuous explanatory variables; number of years form the first study, time on CMV before start of the study, gestational age and birth weight. Two studies dominate these figures, signified by their size relative to the weight they received in the analyses [19;20]. Furthermore, relatively

Table 1.

Study	*Year*	*Time on CMV*	*Gest. Age*	*Birth Weight*	*SensorM*	*HLVS*	*LPVS*	*Surf*	*CLD lnRR*	*Weight*	*Death or CLD lnRR*	*Weight*
Clark	1992	9.0	28	1.100	Y	Y	N	N	-1.29	0.01	-0.58	0.01
Gerstmann	1996	3.0	31	1.500	Y	Y	N	Y	-0.67	0.04	-0.55	0.02
Wiswell	1996	7.2	27	0.950	Y	N	N	Y	0.02	0.01	-0.23	0.10
Keszler	1997	8.0	27	1.020	N	Y	N	Y	-0.70	0.03	0.48	0.03
Rettwitz	1998	1.0	28	1.100	N	N	N	Y	0.00	0.00	0.31	0.00
Plavka	1999		26	0.850	Y	Y	N	Y	-1.03	0.01	-0.74	0.01
Thome	1999	0.5	27	0.870	N	Y	Y	Y	0.09	0.06	0.01	0.04
Durand	2001	2.6	26	0.840	Y	Y	Y	Y	-0.98	0.02	-0.59	0.02
Moriette	2001	0.3	28	0.990	N	Y	Y	Y	-0.20	0.05	-0.06	0.05
Courtney	2002	2.7	26	0.850	Y	Y	Y	Y	-0.06	0.16	-0.22	0.13
Johnson	2002	1.0	26	0.850	N	Y	Y	Y	-0.01	0.54	-0.02	0.60
Reempts	2003	1.0	29	1.200	Y	Y	Y	Y	0.32	0.03	0.27	0.04
Schreiber	2003	14.0	27	0.980	Y	Y	Y	Y			-0.04	0.05
Craft	2003		26	0.726	N	Y	Y	Y	0.10	0.05	0.09	0.03
Vento	2005	0.3	27	0.880	N	Y	Y	Y	-1.44	0.01	-1.20	0.00

Year: Number of years after the first included study. Time CMV: Mean time on CMV before start of the study in hours. Age: Mean gestational age (weeks). Weight: mean birth weight (kg). HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. Surf: Use of surfactant in the study. CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postmenstrual age. LnRR: Natural log of the relative risk.

Figure 2. Linear regression analyses of Year of Publication

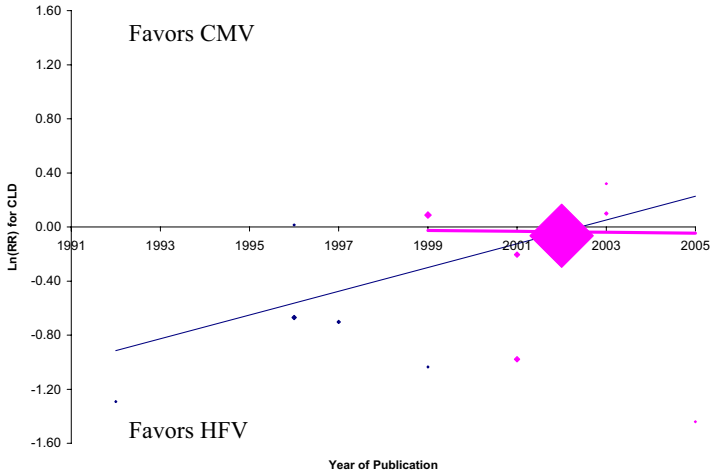
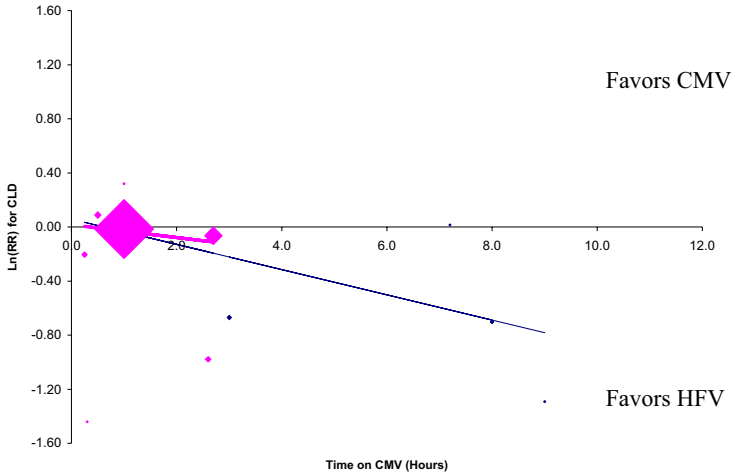
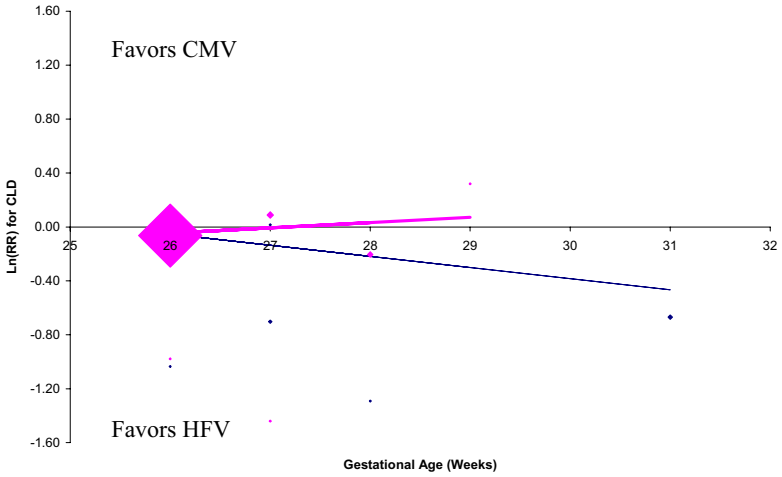


Figure 3. Linear regression analyses of Time on CMV



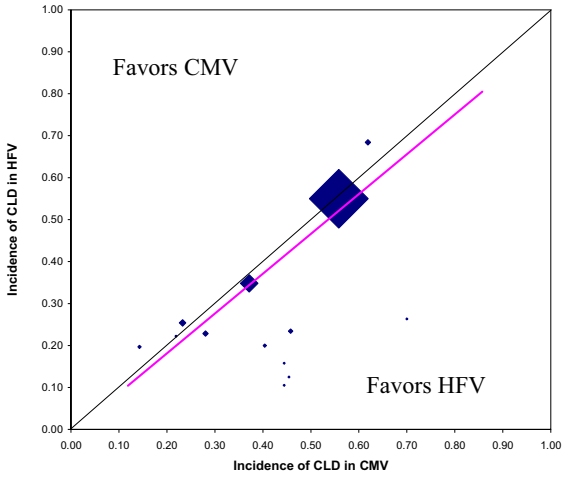
Crude and subgroup linear regression analyses of the effect of year of publication, prior time on CMV and gestational age with natural logarithm of RR of CLD as dependent variable. Y-axis: natural logarithm of the RR. X-axis: explanatory variables. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Thin blue line: regression line including all studies. Thick pink line regression line including only studies with both HLVS and LPVS.

Figure 4. Linear regression analyses of Gestational Age



Crude and subgroup linear regression analyses of the effect of year of publication, prior time on CMV and gestational age with natural logarithm of RR of CLD as dependent variable. Y-axis: natural logarithm of the RR. X-axis: explanatory variables. Blue diamonds: studies with either no HLVS or no LPVS. Pink diamonds: studies with both HLVS and LPVS. Thin blue line: regression line including all studies. Thick pink line regression line including only studies with both HLVS and LPVS.

Figure 5 Incidence of CLD in HFV as a function of incidence of CLD in CMV



Y-axis: incidence of CLD in HFV. X-axis: incidence of CLD in CMV. Thin pink line: regression line including all studies.

Table 3

All Studies

CLD	*Crude B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RRR*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.09	**0.025**	0.01	0.16	3.13	1.18	8.27
SensorM	-0.17	0.351	-0.55	0.21	0.84	0.58	1.24
TimeCMV	-0.09	0.055	-0.19	0.00	0.44	0.19	1.02
Age	-0.08	0.237	-0.23	0.06	0.66	0.32	1.36
Weight	-0.76	0.163	-1.87	0.35	0.54	0.22	1.33
HLVS	-0.11	0.883	-1.74	1.52	0.89	0.17	4.57
LPVS	0.64	**0.009**	0.19	1.10	1.91	1.21	3.00
Surf	1.21	0.168	-0.59	3.00	3.34	0.56	20.03
CMV	-0.18	0.774	-1.53	1.17	0.90	0.42	1.92

Death or CLD	*Crude B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RRR*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.05	0.096	-0.01	0.12	2.01	0.86	4.65
SensorM	-0.17	0.132	-0.39	0.06	0.85	0.67	1.06
TimeCMV	-0.01	0.590	-0.05	0.03	0.92	0.65	1.29
Age	-0.02	0.733	-0.13	0.10	0.91	0.52	1.61
Weight	-0.22	0.611	-1.16	0.71	0.84	0.40	1.77
HLVS	-0.37	0.698	-2.44	1.69	0.69	0.09	5.45
LPVS	0.19	0.275	-0.18	0.56	1.21	0.84	1.76
Surf	0.52	0.289	-0.51	1.56	1.69	0.60	4.75
CMV	-0.02	0.963	-0.91	0.87	0.99	0.60	1.63

Univariate linear regression analyses were calculated for CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postgestational age, and death or CLD. The following co-variates were evaluated: Year: Number of years after the first included study. SensorM: Whether or not a SensorMedics was used. TimeCMV: Mean time on CMV before start of the study in hours. Age: Mean gestational age (weeks). Weight: mean birth weight (kg). HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. Surf: Use of surfactant in the study. B was the estimated crude coefficient. RRR: relative risk rate= RRcovariate=1/RRcovariate=0, for binary variables (SensorM, HLVS and LPVS), for continues variables the extreme values reported in the studies were used, 13 for years, 8.7 for Time on CMV, 5 for Age, 0.8 for Weight and 0.65 for CMV (RRRyears= RRyear=2005/RRyear=1992, RRRtime on CMV= RRtime=9 hours/RRtime=0.3 hours, RRRage= RRage=31 weeks/RRyear=26 weeks, RRRweight= RRweight=1.5 kg/RRyear=0.7 kg, RRRincidence of CLD in CMV= RRincidence=0.75/RRincidence=0.08).

Studies with Surfactant, HLVS and LPVS

CLD	*B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RR R*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.00	0.971	-0.23	0.22	0.96	0.05	17.34
TimeCMV	-0.05	0.698	-0.34	0.25	0.66	0.05	8.75
Age	0.04	0.727	-0.22	0.30	1.22	0.33	4.49
Weight	0.41	0.693	-1.99	2.81	1.38	0.20	9.44

Death or CLD	*B*	*Sig.*	*95% Confidence Interval Lower Bound*	*Upper Bound*	*RR R*	*95% Confidence Interval Lower Bound*	*Upper Bound*
Year	0.01	0.846	-0.15	0.17	1.20	0.15	9.72
TimeCMV	0.00	0.819	-0.05	0.04	0.96	0.65	1.43
Age	0.06	0.406	-0.10	0.21	1.34	0.61	2.92
Weight	0.55	0.396	-0.89	1.99	1.55	0.49	4.90

small outlying studies determined the direction of the coefficients of the regression lines [10;11;13;15;17;24]. Crude estimations of these coefficients showed an increase of the RR over the years to the line of no effect. A decreasing time on CMV prior to study initiation seemed to be related to increasing RRs. Higher gestational age and increase of birth weight seemed to be positively associated with increase of RR.

Figure 5 shows how incidence of CLD in the CMV treated patients related to incidence in HFV treated patients. The diagonal line represents the line of no effect in this figure. A trend line was fitted by weighted linear regression, showing a small effect of change in incidence in CMV on incidence in HFV treated patients.

Univariate meta-regression analyses with relative risk of CLD as dependent variable showed significant associations with year of publication and whether or not a protective ventilation strategy was applied

with CLD (Table 2). In the univariate regression analyses with death or CLD as composite outcome no significant associations were detected. Whether or not a SensorMedics high frequency oscillatory ventilator was used and baseline incidence in CMV treated patients displayed the smallest effects on outcomes (RRR = 0.84 and 0.90 for CLD and RRR = 0.85 and 0.99 for death or CLD, respectively).

No change in relative risk for CLD remained over years of publication in the subgroup of studies with HLVS, LPVS and concomitant use of surfactant and a smaller increase in relative risk for death or CLD (RRR = 0.96 and RRR = 1.20, Table 2 and Figure 2). Opposite effects of gestational age (RRR = 1.22 for CLD and 1.38 for death or CLD versus RRR = 0.66 for CLD and 0.91 for death or CLD respectively) and birth weight were detected in the subgroup analysis (Table 2 and Figure 4). Prior time on CMV exerted less effect on outcome compared with the crude

Table 4

Model A

CLD	*Adjusted*		*95% Confidence Interval*			*95% Confidence Interval*	
	B	*Sig.*	*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	-0.66	0.900	-13.03	11.70			
SensorM	-0.04	0.884	-0.75	0.66	0.96	0.47	1.94
TimeCMV	-0.02	0.903	-0.38	0.34	0.85	0.04	19.22
Age	0.03	0.850	-0.36	0.42	1.17	0.16	8.32
HLVS	-0.88	0.306	-2.80	1.04	0.42	0.06	2.84
LPVS	0.70	0.506	-1.73	3.14	2.02	0.18	23.12

Death or CLD	*Adjusted*	*Sig.*	*95% Confidence Interval*			*95% Confidence Interval*	
	B		*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	-1.86	0.412	-7.22	3.49			
SensorM	-0.17	0.309	-0.55	0.21	0.85	0.58	1.24
TimeCMV	0.01	0.722	-0.05	0.06	1.07	0.68	1.69
Age	0.08	0.299	-0.09	0.25	1.47	0.62	3.47
HLVS	-0.88	0.407	-3.38	1.62	0.42	0.03	5.06
LPVS	0.68	0.127	-0.28	1.65	1.98	0.76	5.19

Model B

CLD	*Adjusted*		*95% Confidence Interval*			*95% Confidence Interval*	
	B	*Sig.*	*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	0.07	0.904	-1.21	1.35			
SensorM	-0.06	0.698	-0.38	0.26	0.94	0.69	1.30
HLVS	-0.81	0.203	-2.14	0.52	0.44	0.12	1.68
LPVS	0.72	**0.011**	0.21	1.23	2.06	1.23	3.43

Death or CLD	*Adjusted*	*Sig.*	*95% Confidence Interval*			*95% Confidence Interval*	
	B		*Lower Bound*	*Upper Bound*	*RRR*	*Lower Bound*	*Upper Bound*
(Constant)	0.31	0.706	-1.47	2.09			
SensorM	-0.11	0.318	-0.33	0.12	0.90	0.72	1.13
HLVS	-0.79	0.363	-2.66	1.08	0.45	0.07	2.93
LPVS	0.46	0.089	-0.09	1.01	1.59	0.92	2.74

Multivariate linear regression analyses were calculated for CLD: Chronic Lung Disease, defined as on oxygen at 30-36 weeks postgestational age, and death or CLD. The following co-variates were evaluated: SensorM: Whether or not a SensorMedics type of HFV was used. TimeCMV: Mean time on CMV before start of the study in hours. HLVS: High lung volume strategy in the HFV group. LPVS: Lung protective ventilation strategy in the CMV group. B was the adjusted estimated coefficient. RRR: relative risk rate= RRcovariate=1/RRcovariate=0, for binary variables (SensorM, HLVS and LPVS), for continues variables the extreme values reported in the studies were used, 8.7 for Time on CMV (RRRage= RRage=31 weeks/RRyear=26 weeks).

analysis, RRR = 0.66 for CLD and 0.96 for death or CLD and RRR = 0.44 for CLD and 0.92 for death or CLD in the adjusted and crude analyses respectively (Table 2 and Figure 3).

Multivariate regression analyses were conducted to assess the independent contributions to change in RR by explanatory variables (Table 3). Year of publication was not considered as an independent explanatory variable but rather as proxy for changes in treatment and patient population. Gestational age and birth weight were collinearly related by nature; only gestational age was fitted in the model. One study contributed to the fact that surfactant was not used; therefore, surfactant was not used in the multivariate regression analyses. Two models were fitted. Generally, the resulting estimates showed large confidence intervals. Model A used

SensorMedics, time on CMV, gestational age, HLVS and LPVS as covariates. The largest estimated effects were caused by ventilation strategies, HLVS and LPVS, adjusted for use of SensorMedics ventilator, prior time on CMV and gestational age. These estimations were consistent for the outcomes CLD (RRR = 0.42 and RRR = 2.02 for HLVS and LPVS respectively) and death or CLD (RRR = 0.42 and RRR = 1.98 fro HLVS and LPVS respectively). Use of a SensorMedics ventilator seemed to have a much smaller effect on RR for outcome. The RRR of gestational age, comparing 26 weeks with 31 weeks, for CLD and death or CLD were larger (RRR = 1.17 and RRR = 1.47). The effect of a difference in prior time on CMV of 8.7 hours on CLD versus death or CLD was not consistent (RRR = 0.85 and RRR = 1.07).

As the effects of gestational age and time on CMV were susceptible to small studies with outlying results, a sensitivity analysis was conducted by fitting a second model (Model B) with the most important variables, HLVS and LPVS combined with whether or not a SensorMedics ventilator were used. The reported RRRs were comparable with those in the first model. Type of ventilator did not have a large effect compared with ventilation strategies (RRR = 0.94 and RRR = 0.90). HLVS was associated with a decrease of the RRs comparing HFV with CMV (RRR = 0.44 and RRR = 0.45), while LPVS increased the RRs to the line of no effect (RRR = 2.06 and RRR = 1.59).

Discussion

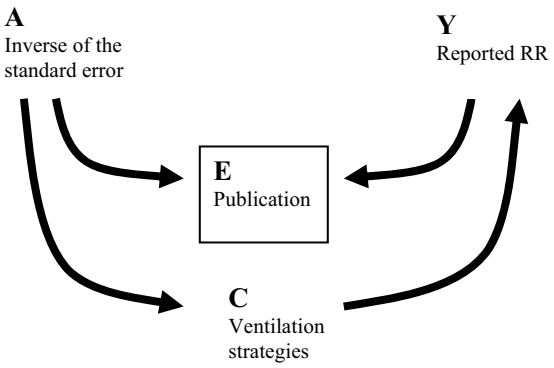
Meta-regression analysis showed a clear trend of decreasing differences in pulmonary outcome between HFV and CMV in randomized trials conducted in premature neonates with IRDS. The most likely hypothesis for this trend was the application of a LPVS in the most recent studies. Use

of surfactant could also have a significant contribution, but only one study did not use surfactant [10]. This made it more difficult to ascertain the effect of surfactant on the change of RR.

In this meta-analysis we evaluated in a quantitative way a number of hypotheses that were raised in randomized trials to account for different results. A relatively large proportion of well conducted trials were available for the analyses. For most explanatory variables there were important differences between trials. The effects of the two most important covariates, HLVS and LPVS, were consistent in the different models and were even increased in effect size by adjusting for other covariates. None of the competing hypothesis were more likely to influence results as shown by calculating the RRRs. However, inferences should be made with caution due to a large amount of uncertainty.

Publication bias was considered unlikely as an explanation of the apparent diminishing relative effect of HFV. Publication bias is selection bias as explained in Figure 6. If only large studies or studies with significant results would be published, then conditioning on only published studies (i.e. selection bias) would result in a relation between study size and reported RR indicating publication bias. However, if larger studies were also associated with changes in ventilation strategies and these strategies resulted in changes in reported RRs, the assumed publication bias would be in fact a real association. Therefore, we conditioned the association between precision and effect size, presumably caused by publication bias, on ventilation strategies. This resulted in a much lower p-value for publication bias. Thus, what appeared to be publication bias was probably due to differences in ventilation strategies related to both study size and observed relative risks.

Figuur 6. Directed Acyclic Graph (DAG) of Publication Bias



A: exposure, Y: outcome, E: common effect, C: confounder. Selection bias is caused by conditioning on the common effect (study being published) of study size/precision and the reported RR. When there is no conditioning on whether or not studies are preferentially published, there is no association. However, if study size and ventilation strategies would be associated and ventilation strategy would be related to RR as well, selection bias could be inferred but in reality not exist.

Other alternative hypotheses that have been formulated to explain differences between studies were also less compatible with the evidence [7]. The type of ventilator, SensorMedics versus other types of high frequency ventilators, displayed low RRR close to one. In the crude analyses, prior time on CMV before study initiation showed contradictory effects to what was hypothesized [8]. The adjusted analyses showed conflicting results depending on the outcome. Therefore, confounding effects of prior time on CMV on HLVS or LPVS could not be established. Gestational age and birth weight could also influence the magnitude of the effect of HFV compared with CMV. Again, a counterintuitive effect was seen in the crude analysis. In the adjusted analysis gestational age did not change the RR for CLD but showed an increase of the RR for less premature neonates. Finally an increased risk of CLD could increase the relative benefit of

HFV. Susceptibility for CLD was estimated using the incidence of CLD in CMV treated patients. Increase in incidence of CLD in CMV was not accompanied by larger RRs comparing HFV with CMV.

The observed effects of continuous variables like time on CMV or gestational age could be exaggerated by small studies with outlying results. However, the meta-regression analysis we conducted was weighted by the inverse variance of the studies. Still, the magnitude of effect could be overstated. For the covariate, time on CMV, the two largest studies showed results that were compatible with the hypothesis that this had no important impact on the results of these trials [19;20]. The same applied to the effect of baseline incidence of CLD or death or CLD. Gestational age and weight were comparable between the two largest trials which made it more difficult to ascertain the relevance of the hypothesis that in smaller and more premature infants HFV performed better than CMV treatment. The observed direction of the effect of gestational age and birth weight, however, was opposite to what the hypothesis predicted. If gestational age was to be interpreted as a higher risk of acquiring CLD, one would expect that an increase in the incidence of CLD was associated with a relatively lower incidence of CLD in HFV treated patients. However, linear regression analysis showed perfectly equal increase in both treatment groups.

Similar findings of the effects of ventilation strategies have been reported by us and other authors as well [2;3]. However, meta-analyses are subject to bias when differences between trials are used to explain differences in reported RRs. In this meta-regression analysis we were able to estimate adjusted association measures, thereby, diminishing the effects of possible confounders. By calculating less biased estimates of the effects of ventilation strategies and the effect of using a SensorMedics ventilator instead of other ventilators on the outcome in the different HFV trials we

were able to reinforce the hypothesis that ventilation strategies are more important than type of ventilator to prevent CLD.

The major advantage of HFV to CMV is delivery of smaller tidal volumes to an optimally recruited lung. Assuming that there is a safe window in the pressure volume curve of a lung between a lower zone with atelectasis and a upper zone with over-distension, surpassing this zone would result in either cyclic recruitment and de-recruitment, over-distension, or both. As this meta-regression analysis did not confirm that subgroups of more premature neonates, avoidance of CMV prior to initiating HFV, or neonates with higher risk of CLD were more likely to benefit form elective HFV in IRDS, future research should be directed at identifying patients in which the safe window becomes too small to harbour tidal volumes delivered by CMV.

In conclusion, confining randomized trials to smaller or more premature children with IRDS did not seem to result in better pulmonary outcomes of HFV compared with CMV. A generally held opinion that a prolonged ventilation time on CMV prior to initiating HFV diminished the benefits of HFV was not in agreement with the current evidence. The most important effects resulting in differences between trials were probably caused by ventilation strategies applied in HFV and CMV treated patients.

Appendix

Oxygenation Index = (FiO2*MAP*100) / paO2, where: FiO2 = Fraction of inspired oxygen, paCO2 = Pressure of arterial carbon dioxide, paO2 = Pressure of arterial oxygen, SaO2 = Arterial oxygen saturation.

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