Respiratory tract infection: prevention, early detection and attenuation of immune response

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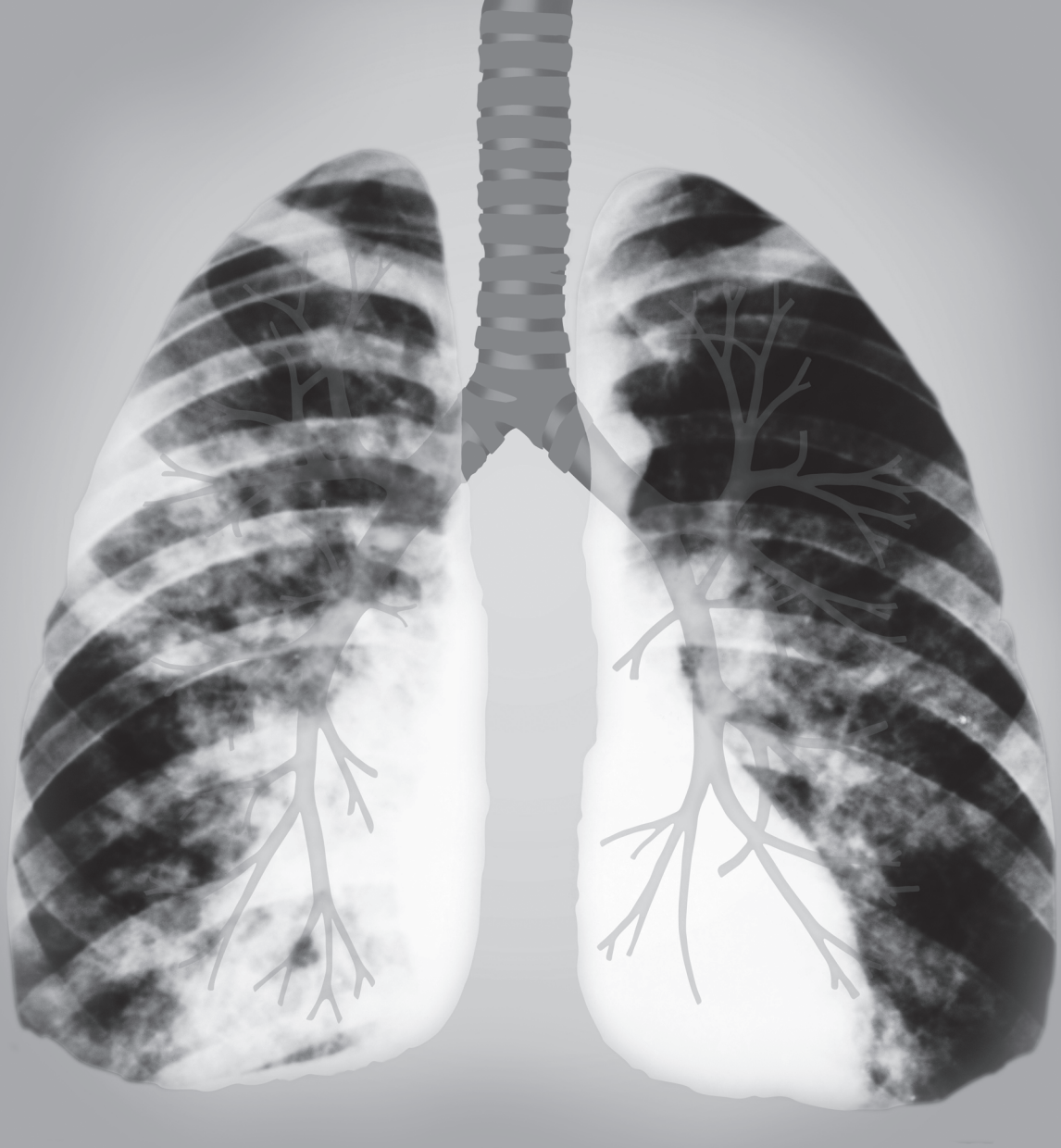

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Influenza season and ARDS after cardiac surgery.

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This chapter was published as a letter:

N Engl J Med 2018; 378:772-773

INTRODUCTION

A pulmonary inflammatory response after cardiac surgery was described almost 60 years ago as a severe complication of such surgery (1). Still, this Acute Respiratory Distress Syndrome (ARDS) is considered life-threatening with a mortality rate of about 40 % of those affected (2, 3). The pathogenesis of ARDS is complex and not all factors involved are elucidated (4).

One "massive hit" may cause ARDS but it seems more likely that ARDS follows on multiple sequential minor insults (5, 6). Cardiopulmonary bypass (CPB) might be the most important factor causing ARDS postoperatively (7). Transfusion of blood products, complexity of surgery and emergency procedures are additional insults or risk factors (3, 8). Most of these factors are rigid and do not lend to intervention, in an effort to improve outcome after surgery.

Recently, it has become clear that symptomatic viral infections may cause acute lung injury. In particular, severe, symptomatic influenza virus infection can lead to ARDS (9, 10).

Most influenza virus infections in adults, however, are asymptomatic. Thus, in a recent analysis, only 23 percent of influenza virus infections were symptomatic (11).

Moreover, an asymptomatic respiratory virus infection has been demonstrated in a small cohort of patients undergoing elective cardiac surgery (12). Such asymptomatic infections could be a hit contributing to the development of ARDS, e.g. by inducing a low-grade inflammatory response in the lung priming this organ for ARDS in case additional insults would follow.

The aim of the present study was to fill in this deficit and to test in adults, respiratory virus infections as a risk factor for development of ARDS after cardiac surgery.

METHODS

A single-center observational cohort study based on routinely collected clinical data was conducted at the Intensive Care Unit (ICU) of the Leiden University Medical Center (LUMC) between January 2009 and December 2011. This is a tertiary university hospital in the larger metropolitan area of the Netherlands. The ICU is a 25 bed, mixed medical, surgical, neurosurgical and thoracic surgical ICU. All patients ≥ 18 years of age were enrolled at admission on the ICU after cardiac surgery.

The study was approved by the Medical Ethical Committee of the Leiden University Medical Center.

Primary outcome was ARDS within 7 days after cardiac surgery, according to the Berlin definition (13). Secondary outcomes were time on mechanical ventilation, length of stay in ICU and ICU mortality.

Elective cardiac surgery patients were admitted to the hospital one day prior to surgery and were checked to be fit for surgery. In case of fever or clinically apparent respiratory tract infection on the day of surgery, the operation was postponed. A minority of patients underwent surgery in an emergency setting. These patients were not checked for fever or severe respiratory tract infections since their cardiac emergency was life-threatening and therefore warranted immediate surgery.

Cardiac surgery involved coronary artery bypass grafting (CABG), ventricular surgery, valve surgery or aortic surgery.

Induction of anesthesia was done with propofol and remifentanil. Anesthesia was maintained with midazolam or propofol and remifentanil and sufentanil. Tranexamic acid prophylaxis was given to minimize perioperative blood loss, cefazolin was used as antibiotic prophylaxis.

Cardiopulmonary bypass (CPB) with a centrifugal blood pump was initiated. Oxygenation was ensured with a hollow fiber membrane oxygenator, tubing was coated with bio-inert heparin-free polymers. Flow was laminar. Intermittent warm antegrade blood cardioplegia was instituted. During CPB, heparin was used to achieve an activated clotting time > 400s. Patients were ventilated with low pressure and low tidal volume to prevent atelectasis of the lung, except for procedures in which persistent ventilation obstructed surgical procedures. During bypass, core temperature was maintained at 34°C to 36°C. Active cooling was solely used during aortic surgery to prevent brain ischemia. Inotropic and vasoactive agents were administered on indication.

Perioperative care was according to the fast-track protocol (14, 15). During the study period, no changes in protocols of intraoperative mechanical ventilation of cardiac surgery patients have been practiced in our institution. On the ICU, lung protective mechanical ventilation (PEEP 5-8 with small tidal volumes (<6ml/kg) according to the then prevailing mechanical ventilatory standards) has been used.

Demographic data, ASA category, EuroSCORE as preoperative risk assessment (16), APACHE IV score as a marker of severity of disease after surgery (17) were all recorded peri-operatively. Duration of surgery and duration of cardiopulmonary bypass (CPB) were recorded. Administration of blood products was recorded.

Definition of ARDS

Patients were diagnosed with an ARDS if they have met each of the Berlin criteria described below (13):

- Within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Bilateral opacities on chest radiograph or computer tomography scan—not fully explained by effusions, lobar/lung collapse, or nodules
- Respiratory failure not fully explained by cardiac failure or fluid overload
  Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
- Oxygenation:
  - Mild: 200 mm Hg < PaO_2:FiO_2 ratio ≤ 300 mmHg with PEEP or CPAP ≥ 5 cm of water
  - Moderate: 100 mm Hg < PaO2:FiO2 ratio ≤ 200 mm Hg with PEEP ≥ 5 cm of water
  - Severe: PaO2:FiO2 ratio ≤ 100 mm Hg with PEEP ≥ 5 cm of water

Abbreviations: CPAP, continuous positive airway pressure; FiO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Cardiac surgery was the initial clinical insult. All criteria were measured within the first week after cardiac surgery.

Chest roentgenograms were standardly obtained on admission on the intensive care unit (ICU) and 24 hours after admission to the ICU. If the respiratory condition of patients deteriorated, additional radiographic evaluation, including CT scan, was performed. Presence or absence of bilateral opacities was judged by 3 independent observers on chest radiograph or computer tomography scan. The observers were unaware of the study design. Consensus in interpretation was required. In case of discrepancy in radiograph or scan interpretation, uniformity was achieved by discussion between observers. Prominent hili on both sides were not considered as bilateral opacities. This feature is most likely due to cardiac failure and therefore not a feature of ARDS.

Presence of hypoxia and ventilation prerequisites were monitored continuously throughout ICU stay. In case ARDS had developed, the point of time that the patient first fulfilled the Berlin criteria was recorded.

The worst oxygenation during the first week after cardiac surgery was used to determine severity of ARDS.

Assessment of respiratory virus infection

Preoperative respiratory virus diagnostics is not routinely performed, and thus none of our patients was tested for presence of respiratory viruses. Of note, none of the electively operated patients experienced preoperative respiratory complaints or was febrile on admission which would have justified such diagnostics.

Therefore, we have used influenza season as a proxy for respiratory virus infection.

Surveillance of influenza season is conducted by the Netherlands Institute for Health Services Research (NIVEL) and the WHO European Flu Network. They report the number of patients with influenza-like illness (ILI) in the Netherlands (18, 19). NIVEL primary care database assembles records from sentinel general practices in an information system. Data about ILI come from approximately 120,000 patients recorded in these GP practices and represent a good estimate of the Dutch population.

ILI incidence was calculated per 100,000 persons per week between 2009 and 2011 (20). In temperate climate, infections with most respiratory viruses have a seasonal pattern (21-23) and therefore ILI incidence is fluctuating.

In the Netherlands, influenza epidemic season is defined by > 51 ILI-reports per 100,000 per week for at least two consecutive weeks and by the detection of Influenza virus in respiratory samples (24, 25). An epidemic season ends in the first week ILI-reports fall to ≤ 51 per 100,000 per week.

These patients with Influenza A or B virus infection contribute to a large extent to the seasonal increase in ILI numbers. The percentage of positive Influenza specimens is highest during the ILI epidemic season (26), making this the best indicator for Influenza virus activity (27).

In contrast to the well-defined influenza epidemic season, we have arbitrarily predefined a baseline season as at least two consecutive weeks < 25 ILI-reports per 100,000 per week. This represents a period with low incidence of respiratory virus infections. The baseline periods end in the first week ILI-reports increase to ≥25 per 100,000 per week.

All other weeks were categorized as periseasonal period. These periods represent build up phase to an epidemic season or a period of decreasing ILI activity towards a baseline sea-

son. Comparable baseline and periseasonal periods in surveillance of respiratory viruses have been used previously (28).

Statistical analysis

Continuous variables were summarized as either means with standard deviations or medians with interquartile ranges. Categorical variables were depicted as numbers with percentages or as medians with interquartile ranges. Kruskal-Wallis and Chi-squared tests were performed for comparing baseline data as appropriate. Statistical analysis was performed using SPSS (IBM Software) version 23.

To evaluate whether influenza epidemic season is a risk factor for development of ARDS or ICU mortality, we have used binary logistic regression to calculate odds ratio with 95% confidence intervals.

For continuous secondary outcomes (time on mechanical ventilation and length of stay on ICU), we have used mixed linear modelling and calculated estimates with 95% confidence intervals. All variables that were significant ($p<0.1$) in univariate analysis and variables that were deemed clinically relevant were entered in the multivariable logistic model. Emergency procedure or not was not added to the model since both EuroSCORE and APACHE IV score have this entity within their total score.

EuroSCORE is used as preoperative risk assessment and therefore ASA category is not added to the model.

RESULTS

Between January 2009 and December 2011, in total 2021 patients have undergone cardiac surgery. Of these patients, 8 died during surgery and therefore 2013 were admitted to the ICU postoperatively.

Of these patients, 289 have had surgery during an influenza epidemic season and 740 during a baseline period. The other 984 patients have had surgery during a periseasonal period.

The patient characteristics are shown in Table 1. Patients and research team had no influence on the season of surgery.

No differences were found in demographic and perioperative variables between the different seasons.

The weeks with different influenza-like illness incidence are specified in Figure 1.

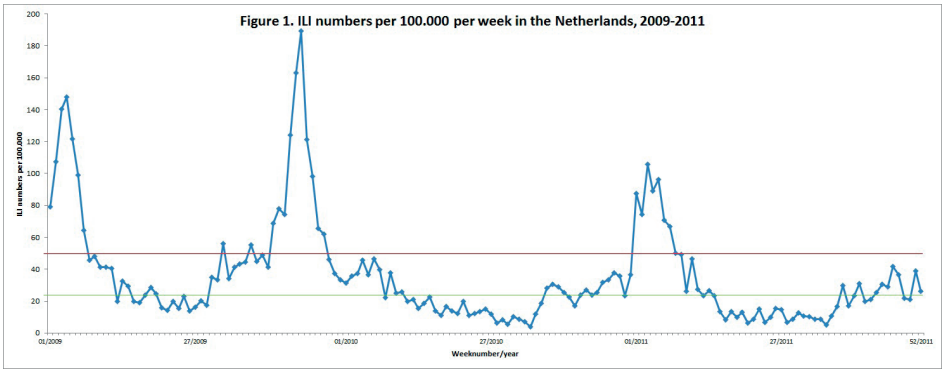

Figure 1. ILI numbers per 100.000 per week in the Netherlands, 2009-2011
The Netherlands Institute for Health Services Research (NIVEL) reports its data on influenza-like illness (ILI) to the WHO European Influenza network. Graphs depict ILI-reports between late 2008 until the end of 2011. The horizontal lines denote baseline (green) and epidemic (red) threshold within the studied period.

Two influenza epidemic seasons were present in 2009 (Fig. 1). The first started in January and a second started in October. The subsequent year 2010 had no influenza epidemic period. In 2011, influenza epidemic season started in January.

Of all patients who had been admitted on ICU after cardiac surgery in baseline weeks, 38 out of 740 (5.1%) developed ARDS. In periseasonal period, 55 out of 984 (5.6%) developed ARDS and in influenza epidemic season 26 out of 289 (9.0%) developed ARDS. All ARDS cases occurred within 26 hours after start of surgery. Of all ARDS patients that underwent surgery during influenza epidemic season, 22 (85%) were admitted within 24 hours before surgery. In the univariate analysis (table 2A and 2B), the odds ratio for ARDS within 7 days after cardiac surgery in influenza epidemic season versus baseline season is 1.83 (95% confidence interval 1.09-3.07).

In the multivariate model (table 3A), odds ratio for ARDS in influenza epidemic season versus baseline season is 1.85 (95% CI 1.06-3.23). Furthermore, duration of mechanical ventilation was significantly increased in the influenza epidemic season compared to the baseline season (Table 3B). Other clinical outcome parameters did not differ significantly between baseline and influenza season (Table 3A and 3B).

Table 1. Demographic data and perioperative details of studied population

Variable*	Baseline season	Periseasonal	Influenza season	P value**
All patients – no.	740	984	289	
Preoperative				
Age in years (IQR)	66 (58-74)	66 (58-75)	66 (58-73)	0.88
Gender - % males	72.2%	67.8%	67.1%	0.10
Body Mass Index - kg/m^2 (IQR)	26 (24-29)	26 (24-29)	26 (24-29)	0.92
ASA category (IQR)	3 (3-3)	3 (3-3)	3 (3-3)	0.68
Emergency procedure (%) EuroSCORE (IQR)	21 (2.8%) 4 (2-9)	27 (2.7%) 4 (2-9)	9 (3.1%) 5 (2-9)	0.95 0.56
During surgery				
Duration of surgery – min (IQR)	360 (300-426)	358 (302-427)	354 (292-428)	0.81
Duration of CPB – min (IQR)	129 (99-184)	131 (94-185)	124 (92-183)	0.79
Units of blood products during procedure (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.70
CABG (%)	435 (58.8)	597 (60.7)	167 (57.8)	0.59
Valve surgery (%)	295 (39.9)	403 (41.0)	115 (39.8)	0.88
- 1 valve (%)	195 (26.4)	279 (28.4)	73 (25.3)	
- 2 valves (%)	91 (12.3)	106 (10.8)	34 (11.8)	
- 3-4 valves (%)	9 (1.2)	18 (1.8)	8 (2.8)	
Aortic surgery (%)	80 (10.8)	109 (11.1)	39 (13.5)	0.45
Left ventricular reconstruction (%)	31 (4.2)	36 (3.7)	12 (4.2)	0.84
Postoperative				
Apache IV score (IQR)	48 (37-59)	48 (38-60)	48 (39-61)	0.74
Second surgery required (%)	63 (8.5%)	64 (6.5%)	22 (7.6%)	0.29

IQR = Interquartile range; min = minute; no. = number
*Medians are described for all continuous variables ** Kruskal-Wallis and Chi-squared tests were performed for comparison of baseline data as appropriate.

Post hoc analysis revealed that the number of ARDS cases increases when Influenza A and B circulation in the community per influenza epidemic season increases (Figure 2). This is calculated by multiplying the total number of ILI cases per 100,000 per epidemic season with the percentage of Influenza A and B positive tests.

DISCUSSION

Cardiac surgery during influenza season is an independent risk factor for development of postoperative ARDS compared to surgery during seasons with little respiratory virus transmission.

Table 2A. Univariate analysis of demographic and perioperative parameters for ARDS and mortality

	ARDS within 7 days after surgery			Mortality on ICU		
	OR	95% CI	P	OR	95% CI	P
Age	1.00	0.98-1.01	0.52	1.02	0.99-1.04	0.22
Sexe	1.02	0.68-1.52	0.92	0.95	0.49-1.82	0.87
BMI	1.03	0.99-1.07	0.21	1.00	0.94-1.08	0.91
Apache IV	1.03	1.03-1.04	0.00	1.06	1.05-1.07	0.00
Euroscore	1.04	1.03-1.06	0.00	1.07	1.05-1.09	0.00
Time in surgery (minutes)	1.00	1.00-1.00	0.00	1.01	1.00-1.01	0.00
Blood products during surgery	1.07	1.04-1.10	0.00	1.10	1.06-1.14	0.00
Total time on CPB (minutes)	1.01	1.00-1.01	0.00	1.01	1.01-1.01	0.00
Emergency procedure	3.15	1.51-6.58	0.00	3.62	1.25-10.47	0.02
ASA 3*	4.21	1.32-13.40	0.02	3.39	0.46-25.09	0.23
ASA 4 and 5*	5.88	1.71-20.18	0.01	14.79	1.94-112.59	0.01
Periseasonal**	1.09	0.72-1.67	0.68	1.19	0.60-2.33	0.62
Influenza epidemic season**	1.83	1.09-3.07	0.02	1.48	0.61-3.56	0.39

* ASA 1 and 2 are the reference category.
** Baseline season is the reference category.

Table 2B. Univariate analysis of demographic and perioperative parameters for time on mechanical ventilation and length of stay on ICU

	Time on mechanical ventilation (hours)			Length of stay on ICU (hours)		
	Estimate	95% CI	P	Estimate	95% CI	P
Age	0.39	-0.24-1.02	0.23	0.39	-0.26-1.04	0.24
Sexe	4.09	-12.21-20.38	0.62	4.43	-12.63-21.48	0.61
BMI	0.58	-1.20-2.36	0.53	0.50	-1.40-2.39	0.61
Apache IV	2.17	1.78-2.55	0.00	2.46	2.07-2.86	0.00
Euroscore	3.95	3.13-4.77	0.00	4.64	3.79-5.48	0.00
Time in surgery (minutes)	0.31	0.25-0.38	0.00	0.37	0.30-0.44	0.00
Blood products during surgery	8.66	6.71-10.60	0.00	11.74	9.69-13.80	0.00
Total time on CPB (minutes)	0.40	0.31-0.50	0.00	0.48	0.38-0.57	0.00
Emergency procedure	25.40	-18.85-69.64	0.26	35.13	-12.22-82.48	0.15
ASA 3*	19.32	-6.23-44.87	0.14	26.22	-0.11-52.54	0.05
ASA 4 and 5*	110.23	76.39-144.08	0.00	105.98	72.02-139.95	0.00
Periseasonal**	10.59	-5.73-26.92	0.20	5.83	-11.31-22.97	0.51
Influenza epidemic season**	27.16	3.83-50.50	0.02	25.11	0.59-49.63	0.05

* ASA 1 and 2 are the reference category.
** Baseline season is the reference category.

Table 3A. Multivariate analyses of demographic and perioperative parameters for development of ARDS and mortality on ICU

	ARDS within 7 days after surgery			Mortality on ICU		
	OR	95% CI	P	OR	95% CI	P
Apache IV	1.03	1.02-1.04	0.00	1.05	1.04-1.07	0.00
Euroscore	1.02	1.00-1.04	0.07	1.03	1.01-1.06	0.01
Time in surgery (minutes)	1.00	1.00-1.00	0.61	1.00	1.00-1.01	0.09
Blood products during surgery	1.00	0.95-1.05	0.93	1.01	0.95-1.08	0.76
Total time on CPB (minutes)	1.00	1.00-1.01	0.25	1.00	0.99-1.01	0.83
Periseasonal*	1.09	0.69-1.72	0.71	0.96	0.43-2.11	0.91
Influenza epidemic season*	1.85	1.06-3.23	0.03	1.57	0.58-4.24	0.37

* Baseline season is the reference category

Table 3B. Multivariate analyses of demographic and perioperative parameters for time on mechanical ventilation and length of stay on ICU

	Time on mechanical ventilation (hours)			Length of stay on ICU (hours)		
	Estimate	95% CI	P	Estimate	95% CI	P
Apache IV	1.61	1.20-2.02	0.00	1.79	1.37-2.20	0.00
Euroscore	1.58	0.64-2.51	0.00	1.69	0.77-2.62	0.00
Time in surgery (minutes)	0.19	0.06-0.31	0.00	0.13	0.02-0.24	0.02
Blood products during surgery	2.80	0.45-5.15	0.02	4.68	2.28-7.09	0.00
Total time on CPB (minutes)	0.00	-0.16-0.16	1.00	0.13	-0.02-0.27	0.08
Periseasonal*	10.00	-5.49-25.49	0.21	6.51	-9.20-22.21	0.42
Influenza epidemic season*	22.64	0.47-44.81	0.05	21.08	-1.42-43.58	0.07

* Baseline season is the reference category.

The main finding of the present study is that the risk for the development of ARDS after cardiac surgery is about twice increased during the influenza season as compared to seasons with low burden of respiratory virus infections. Moreover, the influenza season did increase the duration of mechanical ventilation. The influenza season was estimated on the basis of weekly reporting of influenza-like illness within the community by sentinel surveillance at general practitioner offices, confirmed by detecting influenza in nasopharyngeal samples. On multivariate modelling, the influenza season proved to be an independent risk factor for the development of ARDS postoperatively, besides well-known factors like EuroSCORE and total time on CPB.

Our study has several strengths. Firstly, the database is robust and complete. The definitions used to define an influenza epidemic season and ARDS are widely used and accepted

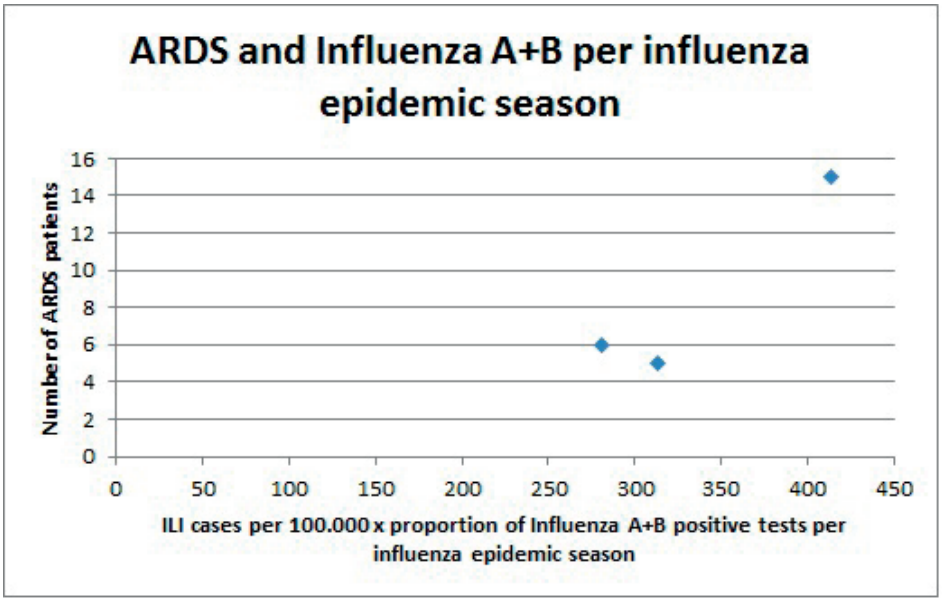

Figure 2. ARDS and Influenza A+B per influenza epidemic season

(13, 18). The ARDS definition by the so-called Berlin criteria makes our results generalizable and readily permissible for comparison with other studies.

Surveillance of influenza-like illness is a good proxy for monitoring burden of influenza virus infection in the community (26, 27). Since our hypothesis is that respiratory virus infection is an extra risk factor for developing ARDS in cardiac surgery patients, our study design is suitable to examine this expectation.

Although previous studies used different definitions of ARDS, the overall percentage of patients developing ARDS in our study (5.9%) resembles that of other studies (3, 8, 29-32).

The in-hospital mortality in patients with ARDS was 17%, which is somewhat less than that reported in other studies (2, 3).

In recent literature, focus on moderate to severe ARDS instead of mild ARDS as a clinically relevant entity has come in use (33). Of note, in our cohort the influenza season was an even stronger risk factor for moderate to severe ARDS than it is for ARDS in general (data not shown).

Our study also has several weaknesses. First and for all, our cohort study shows an association but does not prove a causal relation between viral infection and ARDS in cardiac

surgery patients. There are potential confounders that vary by season, such as vitamin D level or ambient temperature, for which we could not adjust.

The 2009 Influenza A (H1N1) outbreak is remarkable in this aspect. The start of an influenza season in October is uncommon on the northern hemisphere. In this period of the year, temperature was higher than during usual epidemic periods in January to February. In addition, the vitamin D level shortly after summer should have been in the normal range, making these factors as being implicated in ARDS during influenza season less likely.

Still, we cannot exclude that such factors could have confounded our findings (34-36).

Although surveillance of influenza season is robust, the 2009 H1N1 Influenza pandemic might have had an impact on the health seeking behavior of patients. For instance, fear for this new virus infection, might have lowered the threshold for visiting the general practitioner because of respiratory complaints (37, 38) and the definition of influenza epidemic season might have been reached more early. This bias could have underestimated our results.

The number of influenza seasons we studied, three, is too small to draw firm conclusions about secondary outcome variables and the post hoc analysis. Certainly, more influenza seasons with different products of ILI numbers and fraction of Influenza positive tests are required to determine the predictive value for ARDS.

How should we interpret the findings? Studies on the consequences of viral respiratory infection in cardiac surgery patients have mostly been done in the paediatric population. Children with upper respiratory tract infection or with documented rhinovirus infection at the time of cardiac surgery have more postoperative (respiratory) complications (39, 40). On this evidence, it was suggested that an ongoing respiratory virus infection should influence the decision to postpone elective cardiac surgery in children (41). If latent respiratory virus infections are a risk factor for developing postoperative ARDS in adults as well, the chance of developing ARDS can be affected via this risk factor.

Spaeder et al. performed a study in children undergoing cardiac surgery. No differences in postoperative length of stay were detected between ‘viral’ and ‘nonviral’ season. However, in that study the definition of respiratory virus season was much more crude than in our study, their primary end point was different (length of stay) from ours and did not include ARDS, and the sample size was much smaller, making the study underpowered to reveal our association. Furthermore, children with symptomatic viral infections did have an increased risk of morbidity (42). Although viruses in children, their immune response

and seasonality of these viruses are different from that in adults, a comparison of the hypothesis that viral infection is a predictor of worse (respiratory) outcome after surgery is reasonable. To our knowledge, our study is the first to assign respiratory virus season as a risk factor for ARDS in adult patients undergoing cardiac surgery.

H1N1 Influenza virus infections were predominant in the influenza outbreak in October 2009 (23, 43). These infections are therefore presumably the most likely agents contributing to the increase in ARDS.

Our post hoc analysis is in line with this observation. Numbers of ARDS are higher during seasons with relatively more Influenza virus, defined as the ILI numbers multiplied by the proportion of Influenza A and B positive tests per week. This implicates the Influenza virus as the risk factor for ARDS more likely than other factors previously described. Of note, the patients undergoing cardiac surgery were at increased age and therefore less likely to acquire symptomatic H1N1 Influenza virus infection due to cross-reactivity against previously encountered H1N1 Influenza strains (44, 45).

During influenza season, the percentage of positive swabs for other respiratory viruses is relatively high (23, 46). Most likely, other respiratory viruses are equally important risk factors for the increased incidence of ARDS.

Of note, it is well known that symptomatic (H1N1) Influenza virus infection can be a cause of ARDS, with and without prior surgery. However, our study population differs from this group as it does not include patient with manifest respiratory (Influenza or not) virus infection.

Since most patients (97.2%) in our study have had elective surgery, they were checked preoperatively to assess whether they had an (acute) inflammatory disease. Surgery would have been postponed when infection was evident.

Our findings fit with the multiple hit hypothesis of ARDS pathogenesis. ARDS is most likely caused by multiple insults of which cardiac surgery and accompanying cardiopulmonary bypass are the most prominent. This study suggests that asymptomatic respiratory virus infection could prime the lungs for development of ARDS. The finding that ARDS occurs within 26 hours after cardiac surgery reflects our hypothesis that the lungs are primed, perioperatively, by viral infection.

Different studies support this theory.

A controlled randomized study in 1992 revealed that prophylactic antibiotics in patients undergoing aggressive antileukemic chemotherapy, reduced the number of sepsis and ARDS, most likely by removing streptococcal colonization from the upper airways (47). In a rodent model, a low grade immune stimulus in the lungs before pneumonectomy caused aggravated lung injury in the contralateral lung compared to rodents who were not primed with the stimulus (48). The exact mechanism of this lung priming is not elucidated (49).

Previously, we demonstrated in a small cohort that in 18% of elective cardiac surgery patients, respiratory viruses could be detected in mini broncho-alveolar lavage (12). None of these patients had a manifest infection which is in line with a bigger cohort of patients with asymptomatic influenza virus infection (11).

Our population consists of – mostly elderly - cardiac patients, which should have received yearly immunization against influenza viruses. Of all Dutch patients with cardiac illnesses, 77.1 percent was vaccinated against influenza in 2011 (50). Therefore, our study design might be underestimating the association between influenza (season) and ARDS. On the other hand, the influenza vaccine effectiveness is less in older patients and might be insufficient to prevent subclinical influenza replication and infection (about 50% effective in preventing Influenza virus infection in the elderly) and, with that, ARDS (51). Other respiratory viruses with higher incidence during ILI season, for example RS virus, can also be the second hit in causing ARDS.

The majority of patients with ARDS in influenza epidemic season were admitted to the hospital ≤ 1 day before surgery. This essentially excludes nosocomial acquisition of influenza virus in most of the cases.

Future research is needed to test if vaccination of patients could reduce the risk of ARDS post cardiac surgery. Whether vaccination of health care workers could reduce this risk cannot be proven or ruled out by our study. Numbers are too small to draw firm conclusions.

In none of our cardiac surgery patients respiratory virus diagnostics were done before surgery. Remember that none had respiratory symptoms that might have justified such diagnostics.

In the 7 days after cardiac surgery, in only 6 patients respiratory virus diagnostics were done. In none, a respiratory virus was detected and none developed ARDS postoperatively.

Further research will be necessary to reproduce our findings and prospective studies to determine a causal relation is necessary. If confirmed, virus diagnostic testing or vaccination could be useful before high risk cardiac surgery to attenuate the risk of postoperative ARDS.

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