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RESEARCH ARTICLE

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Ovine model of congenital chest wall and spine deformity: From birth to 3 months follow-up

Jesse Shen[1,2] | Nathalie Samson[3] | Jérôme Lamontagne-Proulx[4] | Denis Soulet[4,5] | Yves Tremblay[6,7,8] | Marc Bazin[9] | Charlène Nadeau[3] | Sarah Bouchard[1,2] | Jean-Paul Praud[3] | Stefan Parent[1,2]

[1]Centre de recherche du CHU Sainte-Justine, Department of Surgery, Montreal, Quebec, Canada

[2]University of Montreal, Department of Surgery, Montreal, Quebec, Canada

[3]Neonatal Respiratory Research Unit, Departments of Pediatrics and Pharmacology-Physiology, Université de Sherbrooke, Sherbrooke, Quebec, Canada

[4]Axe Neuroscience, Centre de recherche du CHU de Québec, Quebec City, Quebec, Canada

[5]Faculté de pharmacie, Université Laval, Quebec City, Quebec, Canada

[6]Axe Reproduction, santé de la mère et de l'enfant, Centre de recherche du CHU de Québec, Quebec City, Quebec, Canada

[7]Centre de Recherche en Reproduction, Développement et Santé Intergénérationnelle (CRDSI), Quebec City, Quebec, Canada

[8]Département d'obstétrique/gynécologie et reproduction, Faculté de médecine, Université Laval, Quebec City, Quebec, Canada

[9]Centre de recherche du CHU de Québec, Université Laval, Quebec City, Quebec, Canada

Correspondence
Stefan Parent, CHU Ste-Justine, 3175 Côte-Sainte Catherine, Montréal, QC H3T 1C5, Canada.
Email: parent97@sympatico.ca

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Abstract

Background: The evolution and treatment of lung alterations related to congenital spine and chest wall deformities (CWD) are poorly understood. Most animal models of CWD created postnatally were not evaluated for respiratory function. The goal of our study was to evaluate the effects of a CWD induced in utero on lung growth and function in an ovine model.

Methods: A CWD was induced in utero at 70–75 days of gestation in 14 ovine fetuses by resection of the 7th and 8th left ribs. Each non-operated twin fetus was taken as control. Respiratory mechanics was studied postnatally in the first week and at 1, 2, and 3 months. Post-mortem respiratory mechanics and lung histomorphometry were also assessed at 3 months.

Results: Eight out of 14 CWD lambs (57%) and 14 control lambs survived the postnatal period. One severe and five mild deformities were induced. At birth, inspiratory capacity (25 vs. 32 mL/kg in controls), and dynamic (1.4 vs. 1.8 mL/cmH_2O/kg), and static (2.0 vs. 2.5 mL/cmH_2O/kg) respiratory system compliances were decreased in CWD lambs. Apart from a slight decrease in inspiratory capacity at 1 month of life, no other differences were observed in respiratory mechanics measured in vivo thereafter. Postmortem measurements found a significant decrease in lung compliance—for each lung and for both lungs taken together—in CWD lambs. No differences in lung histology were detected at 3 months in CWD animals compared to controls.

Conclusions: Our study is the first to assess the effects of a prenatally induced CWD on lung development and function from birth to 3 months in an ovine model. Our results show no significant differences in lung histomorphometry at 3 months in CWD lambs compared to controls. Resolution at 1 month of the alterations in respiratory mechanics present at birth may be related to the challenge in inducing severe deformities.

KEYWORDS
deformity, development, growth, in vivo model, pre-clinical models

1 | INTRODUCTION

Congenital spine and chest wall deformities (CWD) can be found in almost one in every 1000 births.[1] Due to space restriction,[2] CWD can hamper lung growth and function to the point of thoracic insufficiency syndrome (TIS).[3] Respiratory insufficiency hence is responsible for the early death of nearly 30% of the newborns with the most severe deformities.[4] Patients who survive the neonatal period may still suffer from TIS as their deformities progress in severity with growth.

Current fusionless surgical implants[5] may present a potential breakthrough in CWD treatment. They however are still controversial because of the various options available as well as the mixed results reported in the literature.[6,7] For instance, the Vertical Expanding Prosthetic Titanium Rib (VEPTR) is associated with a high complication rate and little improvement in pulmonary function.[8–10] We believe that the lack of efficiency of the surgical implants is due to the poor appraisal of their efficacy beforehand in the appropriate animal model of CWD.

Most previous animal studies on the relationships between respiratory mechanics and CWD induced the deformities postnatally.[11–15] As the majority of lung development occurs in utero and during the immediate postnatal period however, results obtained from these animal models cannot completely define the effects of CWD on respiratory function. We previously developed an ovine model of in utero induced CWD to mimic as closely as possible the clinical settings.[16] Our initial proof-of-concept study, which measured lung function at 48 h of life, did not however allow us to define the effects of CWD on lung development. Indeed, contrary to rodents, lung development in ovines is similar to humans, with alveolarization beginning prenatally and finishing postnatally.[17,18] In terms of respiratory mechanics, it is expected that a chest wall deformity would lead to a decrease in chest wall compliance, leading in turn to a decrease in respiratory system compliance. In addition, it is expected that the restricted volume of the rib cage alters lung growth, leading also to a decrease in lung compliance.

The main aim of our study was therefore to confirm the appropriateness of our preclinical model of congenital CWD and to document the natural history of the alterations in respiratory mechanics and lung development in the first 3 months of life.

2 | MATERIALS AND METHODS

The study was carried out in accordance with the recommendations of the Canadian Council on Animal Care. The study protocol was approved by the Ethics Committee for Animal Care and Experimentation of the Université de Sherbrooke (protocol #2019–218). Experiments were conducted in eight CWD and 14 control lambs born at term from nine ewes.

2.1 | In utero creation of the spinal and chest wall deformity

Under general anesthesia (isoflurane 2%, Baxter Corporation, Mississauga, ON, Canada), CWD were induced surgically in utero in 70–75 days old fetuses (normal term of 147 days), as previously described.[18] Briefly, under sterile conditions, a longitudinal laparotomy was performed to expose the uterine horns, and a hysterotomy was performed. The lower limbs, abdomen, and thorax of the fetal lamb were delivered. Then, the seventh and eighth left ribs were localized—by manual counting from the first to the last and vice versa—and resected. Following fetal skin closure, each lamb was returned to the uterus and the amniotic fluid was replaced with warm Ringer's Lactate containing penicillin G (Vétoquinol N-A Inc, Lavaltrie, QC, Canada). The membranes and uterus were closed, followed by the abdominal wall. Once awake, the ewes returned to their pen and were allowed pursuing the remainder of their gestation until they gave birth spontaneously to their offspring.

2.2 | Characterization of the ovine model of spinal and thoracic deformity

The lambs were kept with their mother from birth up to 3 months of life. Since sheep reach puberty toward 6–8 months of age, our study hence encompassed the period with the bulk of postnatal alveolarization. Vital signs—including respiratory rate (RR), heart rate (HR), and transcutaneous oxygen hemoglobin saturation (SpO_2)—and weight were measured monthly. These measurements were performed to detect the development of respiratory insufficiency or failure to thrive in early life. In addition, rib cage dimensions, including spine to xyphoid and spine to sternum lengths, and rib cage width, were measured using a pelvic caliper dedicated to large animals (see Figure 1). Chest x-rays were performed to assess the deformity with the Cobb angle measurements of the main curve.

2.3 | Assessment of respiratory system mechanics

As previously described,[18] respiratory system mechanics were assessed in anesthetized (IV propofol, 6 mg/kg/h, Baxter Corporation, Mississauga, ON, Canada), curarized (one succinylcholine bolus, 2 mg/kg, Teligent Canada, Mississauga, ON, Canada) and ventilated lambs using a Servo-i ventilator (Maquet, Rastatt, Germany). Respiratory measurements were repeated every month in each animal from birth up to 3 months of life. First, the dynamic respiratory system compliance was computed on 10 respiratory cycles in the volume control mode (tidal volume: 10–12 mL/kg, RR: 40/min, PEEP: 0 cmH_2O, FiO_2: 30%). Afterward, the maximal inspiratory capacity was measured by inflating the lungs with a positive pressure of 30 cmH_2O. Finally, the pressure-volume curve of the respiratory system was computed by progressively inflating the lungs from 5 to 20 cmH_2O followed by a stepwise deflation down to 5 cmH_2O. The static compliance was measured at each 5 cmH_2O increment/decrement step. Given that the upper inflection point of the pressure-volume curve was below the 20 cmH_2O pressure level, the static compliance values were averaged without including this level. In this way, our static compliance values are within both the lower (above the functional residual capacity) and upper inflection point. No measurable hysteresis was observed during these measurements.[19]

2.4 | Post-mortem measurement of lung function and histomorphological analysis

All lambs were euthanized at 3 months of age with an overdose of pentobarbital (90 mg/kg, Bimeda, Cambridge, ON, Canada). Following euthanasia, the tracheobronchial tree, lungs, and mediastinum were resected *en bloc* to perform post-mortem respiratory mechanics, as described above, on both lungs and then for each lung individually. Also, CT scans of the spine and chest wall were performed on the lamb carcasses using a Philips Brilliance CT 16-slice scanner with 1-mm slice thickness, and the intrathoracic volume was quantified using the 3D Slicer, version 4 image analysis software[20] (http://www.slicer.org).

Histomorphometric analysis of the lung was performed in all 8 CWD animals and 6 randomly selected control lambs (Figure 2). Following post-mortem respiratory function measurements, the resected

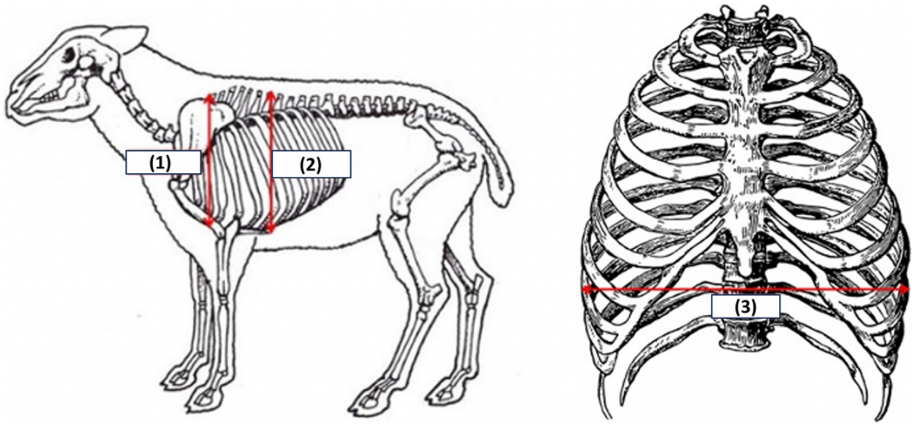

FIGURE 1 Summary of chest wall measurements: spine to sternum (1) and spine to xyphoid (2) lengths, and rib cage width (3).

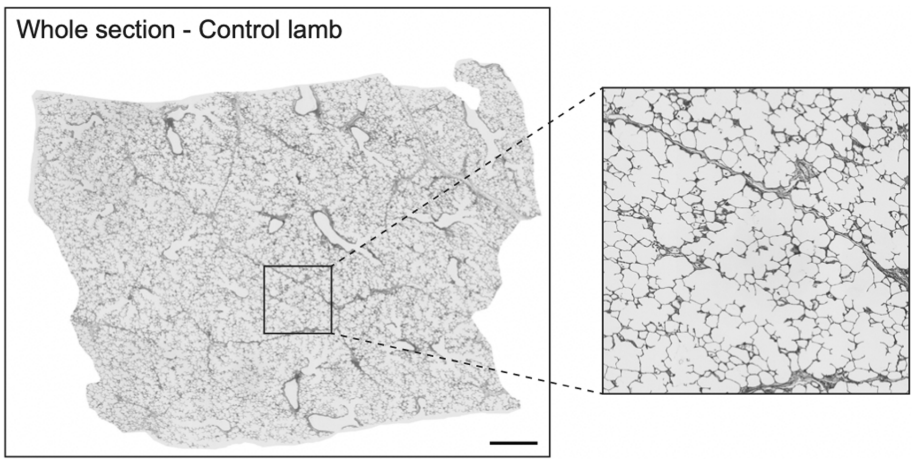

FIGURE 2 Representative scan of a control lamb's lung section used for histomorphometric analysis. Scale bar: 50 µm.

TABLE 1 Cobb angle from birth to 3 months of life in lambs with congenital spine and chest wall deformity.

	Cobb angle at birth (°)	Cobb angle at 1 month (°)	Cobb angle at 2 months (°)	Cobb angle at 3 months (°)
CWD 1	0	0	0	0
CWD 2	0	0	0	0
CWD 3	7.5	0	0	0
CWD 4	10	0	0	0
CWD 5	10	7.5	0	0
CWD 6	13	7.5	7.5	8
CWD 7	13	7.5	7.5	10
CWD 8	51	43	45	45

Note: CWD, each number represents a different lamb.
Abbreviation: CWD, congenital spine and chest wall deformity.

TABLE 2 Comparison of weight, spine to xiphoid, and to sternum lengths, as well as maximal coronal plane width from birth to 3 months between control ($n = 14$) and CWD ($n = 8$) lambs.

	Weight (kg)			Spine to xiphoid length (cm)			Spine to sternum length (cm)			Coronal plane width (cm)		
	CTRL	CWD	*p* value	CTRL	CWD	*p* value	CTRL	CWD	*p* value	CTRL	CWD	*p* value
2–3 days	3.5 ± 0.6	3.8 ± 0.4	0.1	**10.6** ± 0.9	**11.6** ± 0.8	**0.03**	12.3 ± 1.0	12.8 ± 0.4	0.1	7.9 ± 1.4	7.8 ± 1.0	0.8
1 month	9.7 ± 1.8	9.2 ± 1.7	0.8	16.1 ± 1.4	15.6 ± 0.9	0.6	17.4 ± 1.1	17.4 ± 1.2	1.0	14.2 ± 1.5	13.4 ± 1.4	0.3
2 months	17.3 ± 3.2	18.3 ± 4.4	0.4	19.4 ± 1.3	19.2 ± 1.3	0.9	20.2 ± 0.9	20.0 ± 2.0	0.7	18.0 ± 1.2	17.6 ± 1.9	0.8
3 months	31.4 ± 4.1	28 ± 4.4	0.2	**22.9** ± 1.7	**20.7** ± 1.1	**0.001**	23.3 ± 1.6	22.0 ± 1.4	0.06	22.0 ± 2.0	20.3 ± 1.3	0.1

Abbreviations: CTRL, control lambs; CWD, congenital spine and chest wall deformity.

lungs were perfused with 10% formaldehyde diluted in PBS under a pressure of 20 cmH_2O for 1 h, then immerged in 10% formaldehyde at 4°C for a minimum of 72 h. Further tissue preparation was performed as previously described.[21] Following whole lung immersion in 10% formaldehyde, 1 cm^3 of a dependent and a non-dependent region of each pulmonary lobe was removed. The lung samples were then treated with 0.1 M of sodium cacodylate and 1% osmium tetroxide before being embedded in paraffin. Each lung sample was thereafter cut into 3 µm sections and stained with 0.1% toluidine blue before being scanned with a NanoZoomer (20×—11 plans Z—separated by 0.5 µm) (Hammatsu Photonics, Hammatsu, Japan). The resulting files were processed using a high-throughput image analysis workflow previously developed.[21,22] Briefly, the image files were processed on a 24-core Xeon system (Intel, Santa Clara, CA) equipped with a 256 GB RAM and analyzed with Matlab 2014a environment (MathWorks, Natick, MA) in four steps: (1) selection of the regions of interest using a custom-made graphic user interface; (2) automated data extraction from the Hamamatsu NDPI file format at native resolution; (3) image processing (segmentation, object detection and area quantification); and (4) septum quantification. For the present study, the perimeter/area ratio of closed structures with an area between 2500 and 10 000 $µm^2$ and a perimeter size above 200 µm—excluding large and medium vessels, and any other parts that were not an alveolar region—, as well as the number of septa, was quantified. The closed structures were manually drawn in each of 272 images of lung section randomly selected and opened using the NDPITools software.

2.5 | Statistical analysis

All analyses were performed using MATLAB R2018a software. Means and standard deviations were computed. The non-parametric Mann–Whitney *U* test was used, and differences considered significant if $p < 0.05$.

3 | RESULTS

3.1 | Ovine model of spinal and thoracic deformity

A congenital spine and chest wall deformity was induced in utero in 14 ovine fetuses. Eight out of 14 CWD (57%) and 14 control lambs

TABLE 3 CT scan intrathoracic volumes of control and CWD lambs at 3 months of life.

Lamb	Control ($n = 4$) (cm^3)	Deformity ($n = 6$) (cm^3)
1	2281.22	2170.47
2	2188.15	2109.01
3	2059.84	1715.78
4	1471.86	1691.96
5	-	1619.48
6	-	1420.60

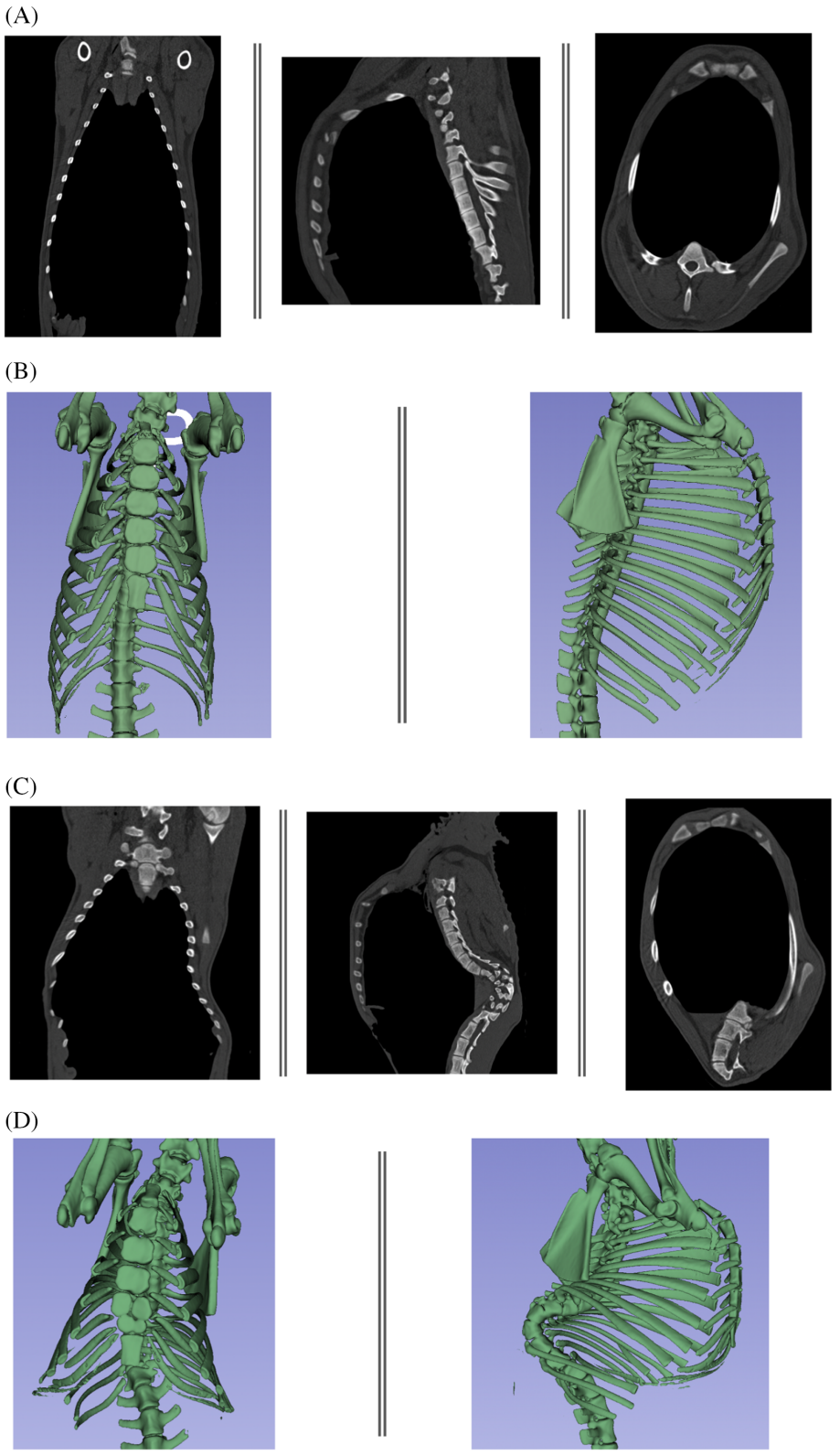

FIGURE 3 CT 3D reconstruction of the rib cage of a control lamb compared to a severe deformity lamb. (A) CT scans of control lamb, (B) CT 3D reconstruction of the rib cage of a control lamb, (C) CT scans of a deformity lamb, (D) CT 3D reconstruction of the rib cage of a deformity lamb.

survived the postnatal period. The causes of death included abortion ($n = 3$), prematurity ($n = 1$), respiratory insufficiency at birth ($n = 1$), and stillbirth ($n = 1$). One severe (51° Cobb angle) and five mild CWD (two with 13°, two with 10° and one with 7.5° Cobb angle) were observed at birth. Two lambs had no measurable deformity at birth. No CWD progressed at 3 months of age (Table 1).

Morphological data are reported in Table 2. The only significant differences were observed for the sagittal spine to xyphoid length. The differences were significant in the first days of life with the CWD animals having a greater spine to xyphoid length compared to controls. No differences were seen at 1- and 2-months follow-up. Significant differences were found at 3 months of age with controls having

TABLE 4 Respiratory system mechanics measured in vivo from birth to 3 months of life in control ($n = 14$) and CWD ($n = 8$) lambs.

	Inspiratory capacity mL/kg			Dynamic compliance mL/cmH_2O/kg			Static compliance mL/cmH_2O/kg		
	CTRL	CWD	*p* value	CTRL	CWD	*p* value	CTRL	CWD	*p* value
2–3 days	32 ± 6.7	25 ± 3.6	0.02	1.8 ± 0.3	1.4 ± 0.2	0.005	2.5 ± 0.4	2.0 ± 0.4	0.005
1 month	28 ± 4.9	24 ± 4.9	0.04	1.3 ± 0.2	1.2 ± 0.1	0.1	1.8 ± 0.2	1.6 ± 0.2	0.3
2 months	21 ± 4.5	19 ± 4.4	0.2	0.8 ± 0.2	0.7 ± 0.1	0.1	1 ± 0.3	1 ± 0.3	0.7
3 months	19 ± 3.1	16 ± 3.9	0.2	0.6 ± 0.1	0.6 ± 0.1	0.1	0.8 ± 0.2	0.8 ± 0.2	0.2

Note: See abbreviations in Tables 1 and 2. *$p < 0.05$.
Abbreviations: CTRL, control lambs; CWD, congenital spine and chest wall deformity.

TABLE 5 Post-mortem measurements of respiratory mechanics at 3 months in control ($n = 14$) and CWD ($n = 8$) lambs.

	Inspiratory capacity mL/kg			Static lung compliance mL/cmH_2O/kg		
	CTRL	CWD	*p* value	CTRL	CWD	*p* value
Total	18.5 ± 6.9	13.3 ± 5.2	0.13	0.65 ± 0.3	0.50 ± 0.3	0.001
Right	8.4 ± 3.4	5.4 ± 1.6	0.02	0.31 ± 0.1	0.23 ± 0.1	0.00001
Left	7.6 ± 3.3	5.6 ± 2.0	0.2	0.28 ± 0.1	0.21 ± 0.1	0.0001

Abbreviations: CTRL, control lambs; CWD, congenital spine and chest wall deformity.

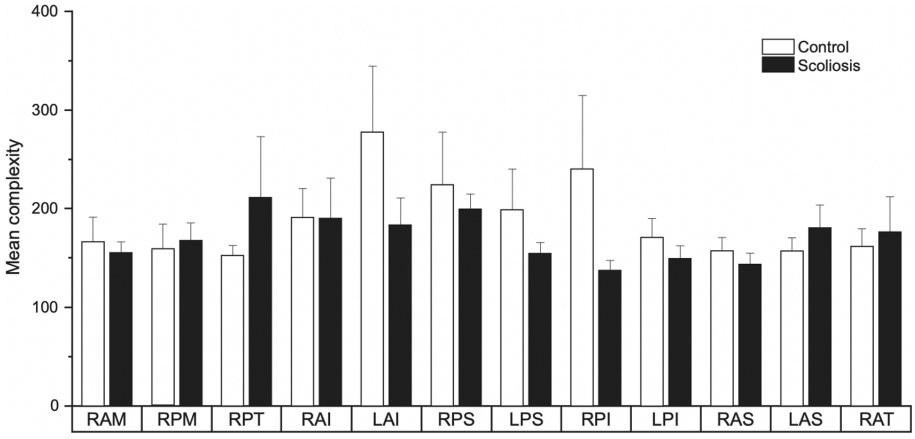

FIGURE 4 Histograms of alveolar complexity analysis, measured as the perimeter/area ratio of closed structures. Various regions of the lungs were used for this histomorphometric analysis in control ($n = 6$) and CWD ($n = 8$) lambs. L, **l**eft; A, **a**nterior; I, **i**nferior; M, **m**iddle, P, **p**osterior; R, **r**ight; S, **s**uperior, T, **t**racheal.

greater length than CWD lambs. No significant differences were observed for weight, spine to sternum length, and coronal plane width between groups.

Post-mortem thoracic volume at 3 months of life computed from chest CT scan was significantly smaller in the six lambs with a severe or mild CWD than in the four control animals (Table 3; $p = 0.0001$). Examples of CT reconstruction are shown in Figure 3.

3.2 | Measurement of respiratory system mechanics

Results for in-vivo respiratory system mechanics revealed that at birth CWD animals had a significant decrease in inspiratory capacity ($p = 0.02$), and in dynamic ($p = 0.005$) and static ($p = 0.005$) respiratory system compliance compared to control animals (Table 4). Thereafter, apart from the inspiratory capacity, which remained decreased at 1 month of life in the CWD animals compared to controls (24 ± 4.2 mL/kg vs. 28 ± 4.9 mL/kg, $p = 0.04$), no other significant differences were noted up to 3 months of life.

Results for post-mortem respiratory system mechanics at 3 months of life revealed that the decrease in inspiratory capacity observed for both and each of the lung was significant only for the right lung in CWD animals. Meanwhile, the static compliance was significantly decreased for both lungs taken as a whole, as well as for each of the right and left lung compared to controls (Table 5).

3.3 | Histomorphometric analysis of lung regions at 3 months

Overall, no differences in alveolar perimeter as well as surface area were observed between control and CWD group. 77% of all alveoli were under 5000 μ^2 of surface area and less than 200 μ of perimeter size. The rest of the alveoli were of variable size. Furthermore, the

complexity of alveoli (perimeter/area) was not significantly different between CWD and control lambs (Figure 4).

4 | DISCUSSION

Results from the present study show alterations in respiratory function and lung development from birth to 3 months in a new congenital CWD ovine model. Despite the persistence of a decrease in respiratory system compliance and in lung and thoracic volume in CWD lambs, no differences in lung histomorphometry were detected between control and CWD lambs at 3 months.

4.1 | Ovine model of spinal and thoracic deformity

Following resection of two ribs between 70 and 75 days of gestation, we observed a variable—from absent to severe—severity of CWD at birth, as documented in our previous pilot study.[18] Conversely to pre-existing postnatal animal models,[11–15] this spectrum mimics CWD in human newborns, who inconsistently present with significant deformity at birth. Most of the prenatally induced deformities in lambs however were mild at birth. The latter could be explained by the fact that most severe deformities of the spine seen in humans are caused by defects in segmentation[23,24] rather than formation (our model). Also, the healing potential of the gestating fetus during the second half of the gestation may have been underestimated.[25,26] This however seems unlikely, for only one lamb had a small portion of one rib grown back, following removal of the entire 7th and 8th ribs along with periosteal bed in all lambs.

Finally, the lesion created by the surgical technique used to induce CWD may not have been important enough to generate severe deformities. However, it remains unclear what caused the fetal losses. Whether it were due to the surgical insult or due to a rapidly progressing deformity in utero are potential hypotheses.

Moreover, all congenital CWD we induced in lambs did not progress at 3 months of age. This is explained as most mild deformities have good prognosis and do not tend to progress.[27,28] This finding supports the notion that mild deformities do not progress and may have good prognosis in terms of lung function. However, the severe deformity lamb also did not progress during the 3-month interval.

Finally, the decrease in rib cage volume that we observed in CWD vs. control animals using CT-scan is consistent with the smaller antero-posterior chest wall measurements in CWD lambs. Lower volumes are seen in patients with thoracic insufficiency syndrome.[3] However, these are mostly seen in severe deformities.

4.2 | Respiratory system mechanics and histomorphometry analysis

As previously observed in our pilot study,[18] CWD animals showed a decrease of 20% in inspiratory capacity, as well as dynamic and static respiratory system compliance at birth. The magnitude of this decrease is less than initially anticipated from our previous pilot results, showing a 60% decrease in respiratory system compliance and a 39% decrease in inspiratory capacity.[18] Such differences can be explained by the two lambs with severe CWD in the pilot study, who also presented with severe respiratory distress at birth, as observed in some human newborns.[3,29]

Furthermore, post-mortem respiratory system mechanics at 3 months of life in CWD lambs revealed a decrease in static compliance for both lungs, as well as for each of the right and left lung. The decrease in lung compliance is likely related, at least partly, to the decreased lung size in CWD lambs, as recently shown in lambs with lung hypoplasia induced by amniotic fluid drainage.[30] Although mild, the decrease in the antero-posterior length of the thorax, in thoracic volume (CT scan), as well as in lung volume and compliance is in line with the concept of thoracic insufficiency syndrome, which relates thoracic volume restriction to decreased lung function.[3]

Although similar intrathoracic volumes were found in control and CWD lambs using CT scan 3D-reconstruction, post-mortem inspiratory capacity and compliance were decreased in CWD lambs. Differences in parenchymal tissue, such as the concentration in elastin or collagen, might be responsible for such decrease. Unfortunately, we do not have any results to confirm our hypothesis. Histomorphometry data does not suggest any differences between both study groups at 3 months of age, when the bulk of alveolarization has expectedly occurred (sheep usually reach puberty and sexual maturity toward 6 months of age). This might be explained by the small number of lambs in each group. Hence, we unfortunately cannot have a definitive conclusion on the presence or not of differences in histological lung development based on our current work.

4.3 | Study limitations

Although our study provides new information on the effects of a prenatally induced mild CWD on lung function and development, several limitations must be mentioned. First, while the variable severity of CWD observed herein in lambs reproduces what is seen in human infants, our ovine model mostly generates mild CWD, as seen by the small number of lambs with persistent CWD at 3 months of age. Of note, however, in the 3 CWD lambs with a Cobb angle between 8 and 45° at 3 months of age, although rib cage dimensions were, on average, not more altered than in the whole CWD group, consequences on respiratory mechanics were more marked. In vivo, measurements indeed showed that the percent decrease in inspiratory capacity (−25% vs. −16%), as well as dynamic (−17% vs. 0%) and static (−13% vs. 0%) compliance of the respiratory system, was greater in these three lambs than in the whole CWD group. The same was observed with post-mortem measurements of the inspiratory capacity of the right lung (−44% vs. −36%), the left lung (−38% vs. −26%) and both lungs (−51% vs. −27%), as well as measurements of static compliance of the right lung (−48% vs. −26%), the left lung (−39% vs. −25%) and both lungs (−57% vs. −23%). Hence, we acknowledge that our ovine

model in its current form does not allow studying the effect of various treatment options to prevent the thoracic insufficiency syndrome, due to the too small number of lambs with severe CWD.[3] We believe however that this work forms the groundwork to further improve this model and to continue to study lung development in a large animal model.

Although the ovine model is frequently used to study neonatal lung function, there are limitations comparing quadrupedal animals to bipedal humans. Quadrupeds such as lambs can move around minutes after birth, which obviously is very different from the supine human newborn who cannot stand during most of the first year of life. How this influences lung growth and function is unknown.

Our accumulated experience in this prenatal ovine model leads us to hypothesize that a CWD induced surgically in the immediate postnatal period in lambs could generate severe CWD, conversely to the later postnatal models designed by other teams.[12] Secondly, the fact that CT scans could be performed post-mortem only—due to logistical challenges related to Q fever prevention—prevented us to measure the evolution of thoracic volumes from birth to 3 months. We however were able to show a decrease in inspiratory capacity, as previously done in animal models.[31] Finally, while it is conceivable that any surgery on the fetus might be stressful enough to impede lung growth, we attempted to decrease this potentially deleterious effect by involving the twin fetuses in the control group.

A limitation of the CT scan analysis was the number of lambs analyzed. Given the logistical challenge related to Q-fever preventive measures when performing postmortem CT scans in lambs, we elected not to image the two CWD lambs who did not have measurable deformity and would likely be closer to controls.

5 | CONCLUSION

This is the first study that evaluates the effects of a prenatally induced congenital spine and chest wall deformity on respiratory system mechanics in an ovine model from birth to 3 months of age. This study showed significant respiratory system mechanics alteration at birth. These differences were not statistically significant at 3 months in vivo, but were noted post-mortem for lung compliance. Moreover, there was no difference in histomorphometry analysis at 3 months between control and CWD lambs. Whether severe deformities generate a proportionally different effect on lung growth and respiratory function remains to be defined.

AUTHOR CONTRIBUTIONS

Jesse Shen: Study design, conceptual framework of study, surgical assistance for in utero surgery, lung function testing and data acquisition, radiographic data acquisition, data analysis, drafting and final approval of manuscript for publication. **Nathalie Samson**: Study design, lung function testing and data acquisition, drafting and final approval of manuscript for publication. **Jérôme Lamontagne-Proulx**: Histological analysis of lung tissue, processing and acquisition of alveolar data, data analysis, drafting and final approval of manuscript for publication. **Denis Soulet**: Conceptual framework of lung tissue and alveoli analysis, methodological design of lung tissue analysis, data analysis, drafting and final approval of manuscript for publication. **Yves Tremblay**: Conceptual framework of lung tissue and alveoli analysis, data analysis, drafting and final approval of manuscript for publication. **Charlène Nadeau**: Assisting surgeries, data acquisition of lung function testing and radiographic data, drafting and final approval of manuscript for publication. **Sarah Bouchard**: Execution of all in utero surgeries for the entire study, drafting and final approval of manuscript for publication. **Marc Bazin**: Data analysis, interpretation of data, creation of figures, drafting and final approval of manuscript for publication. **Jean-Paul Praud**: Study design and development of conceptual framework of the study, data analysis, drafting, revision and final approval of manuscript for publication. **Stefan Parent**: Study design and development of conceptual framework of the study, funding of the study, assistance for in utero surgery, data analysis, drafting and final approval of manuscript for publication.

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CONFLICT OF INTEREST STATEMENT

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ORCID

Jesse Shen https://orcid.org/0000-0001-8241-8934

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