

Stockholm May 9, 2016

Vice-Chancellor Karin Dahlman-Wright
Karolinska Institutet

Notification of Suspected Research Misconduct

RE: Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. Jungebluth P, Macchiarini P. *Lancet*. 2011 Dec 10;378(9808):1997-2004. Epub 2011 Nov 24. PMID: 22119609

Since our filing in August 2014 (1) new data has emerged providing evidence of suspected scientific misconduct and data manipulation on the part of Drs. Jungebluth and Macchiarini. This evidence is sufficient in and of itself to warrant investigation and in our opinion retraction of this dubious article.

On page 1999 in the last paragraph under the section "Results" the Drs. Jungebluth and Macchiarini claim: "5 months after transplantation, the patient is asymptomatic, breathes normally, is tumour free, and has an **almost normal airway** (figure 2C)..." To support the statement of "an almost normal airway" at the time point of 5 months after implantation of the synthetic trachea the authors refer to figure 2A-C on the following page 2000 with the title: "Postoperative follow-up". The figure legend of figure 2C states: "Postoperative volume rendered (VR) image. Air in airways is shown in bright blue. Note that the VR technique displays only the factual air and not the scaffold material. Yellow arrows show borders for scaffold insertion."



Figure 2C in the article, which the authors use to demonstrate "an almost normal airway" at 5 months follow up.

The image in figure 2C is a product of a computed tomography (CT) technique called 3D volume rendering (VR) which incorporates the entire CT data set yielding a 3D display that depicts all tissue types from any orientation (2, 3). According to the radiological archive (table 1) of the patient in question, three radiological examinations were performed in 2011 using the VR technique. All three were performed at Karolinska Huddinge by the same radiologist (4).

The **1st radiological** examination was performed on 2011-05-24 which was 16 days *before* implantation of the synthetic trachea (on 2011-06-09) and must thereby be ruled out as a potential source of the "postoperative follow up" image depicted in figure 2C.

The **3rd radiological** examination was performed on 2011-11-22, which was 5½ months after transplantation and after patient's 1st readmission to Karolinska University Hospital Huddinge on the day before (2011-11-21). According to the authors, the article was submitted with final proofs to *The Lancet* on 2011-11-10 (5, 6) which was 12 days *before* this 3rd examination on 2011-11-22. Consequently this examination also must be ruled out as the source of the image depicted in figure 2C.

Therefore the only possible source of the VR image in figure 2C is the **2nd radiological examination**, which was performed on 2011-07-06, an examination performed not 5 months but only **4 weeks** (27 days) *after* the synthetic trachea implantation on 2011-06-09.

2013-09-16 16:37	Buköversikt CVK inlagd via hö v femoralis med spetsen i höjd med L5, sannolikt övergång v
2011-11-22 09:06	Datortomografi thorax och övre buk Undersökningen är utförd efter i.v. kontrast. Undersökn
2011-07-06 10:04	Datortomografi thorax with high dose iv contrast in three phases TRACHEAL TRANSPLANT Statu
2011-06-23 07:48	Hjärta och Lungor DRYGT 1 cm bred vätskespalt apikolateralt i höger hemithorax. Vätske-luf
2011-06-21 08:23	Lungor liggande Undersökning på avdelning kl 07:55. Jämfört med föregående undersökning 20
2011-06-18 10:24	Lungor liggande Jmf 110617 avlägsning av Bülow-dränet på höger sida. CVK i oför läge med s
2011-06-17 10:29	Lungor liggande På höger sida har spalten mellan pleura och thoraxvägg ökat lateralt jämfö
2011-06-16 14:24	Datortomografi lungartärer Status post trakealtransplantation. Av operationsberättelse fra
2011-06-15 11:04	Lungor liggande Otillräckligt inandningsläge. Den högersidiga pneumothoraxspalten har seda
2011-06-14 00:08	Lungor liggande Jämförs med undersökning från 110612. Knappt 2cm kvarvarande pneumothorax
2011-06-12 19:04	Lungor liggande Det finns en högersidig pleumothorax som apikalt lateralt uppmäts till c:a
2011-06-11 20:32	Lungor liggande Det står stor mängd gas i ventrikeln trots v-sond. Lufthalt har förbättrat
2011-06-11 10:29	Lungor liggande på avd (kl 09.56) Något sämre lufthalt höger ovanlob samt tillskomst av in
2011-06-10 12:16	Lungor liggande IVA kl. 11:50 Jämfört med föregående undersökning tidigare samma dygn har
2011-06-10 01:46	Lungor liggande Ingen pneumothorax. Sedan lungröntgen 2011-06-08 har patienten opererats,
2011-06-08 11:05	Hjärta och Lungor Normalstort hjärta. Normalvida lungkärl. Inga infiltrat. Inga tecken til
2011-06-03 11:10	NM - Demonstration, DT - Demonstration Undersökningen saknar skriftligt svar. Okänt om enb
2011-05-27 12:30	DT - Demonstration, NM - Demonstration Demonstration av PET/CT med 18 FFDG inklusive DT me
2011-05-25 13:32	POSITRONEMISSIONSTOMOGRAFI med 18F-FDG samt DATORTOMOGRAFI efter tillförsel av intravenöst
2011-05-24 13:29	Datortomografi thorax Undersökningen är utan och med i.v. kontrast och med tredimensionell
2011-05-20 12:40	Inga röntgenundersökningar finns. Patienten är bokad för DT thorax Huddinge 2011.05.24 och

Table 1: The patient's radiological examinations at Karolinska University Hospital 2011-05-20 – 2013-09-16 as presented in the radiological archive. The radiological examinations with volume rendering technique (VR) are marked in yellow.

Review of the VR series from the **2nd radiological examination** demonstrates that these images are very similar (figure 1a, b) to the images that Drs Jungebluth och Macchiarini have chosen to use as their 5-month follow up image.

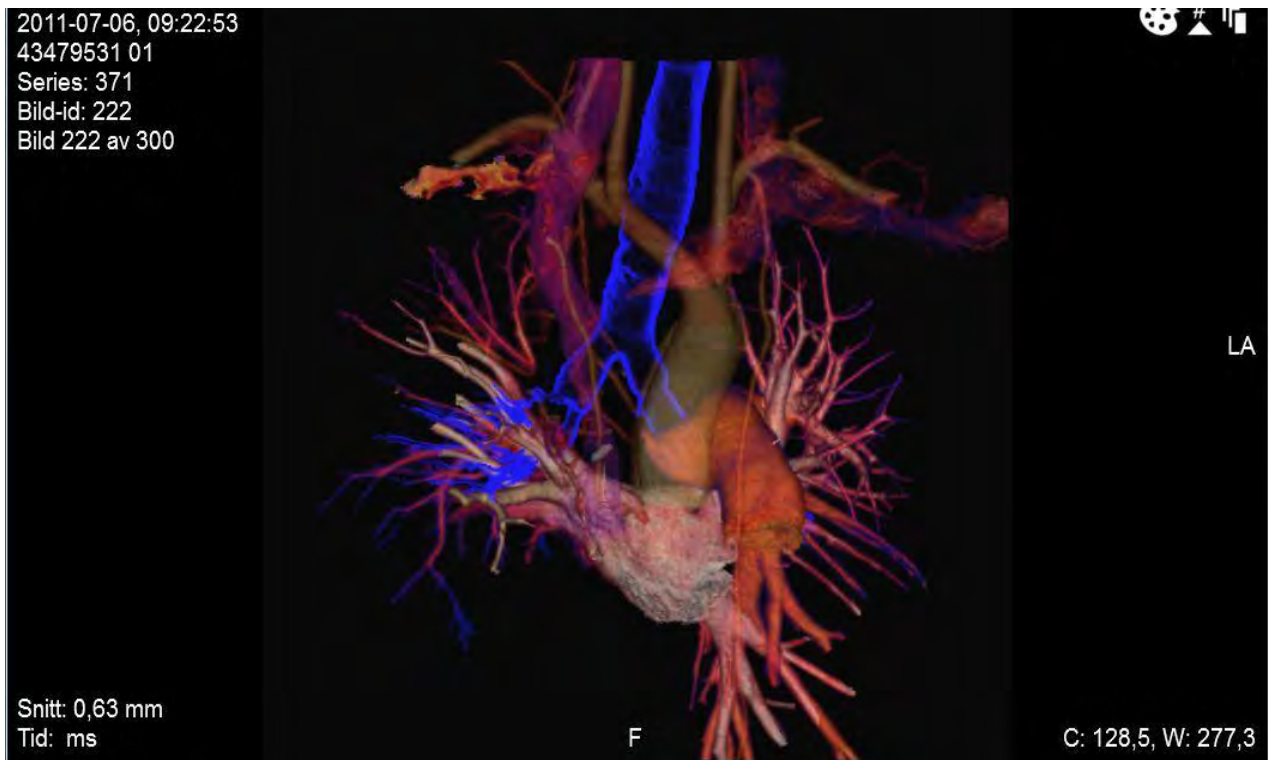


Figure 1a. CT examination 2011-07-06. Example of VR image as documented in the radiological archive. Frontal view. Note the striking similarities with figure 2C in the article above (it is possible to rotate and filter tissue contents in the images which can explain minor differences in perspective).

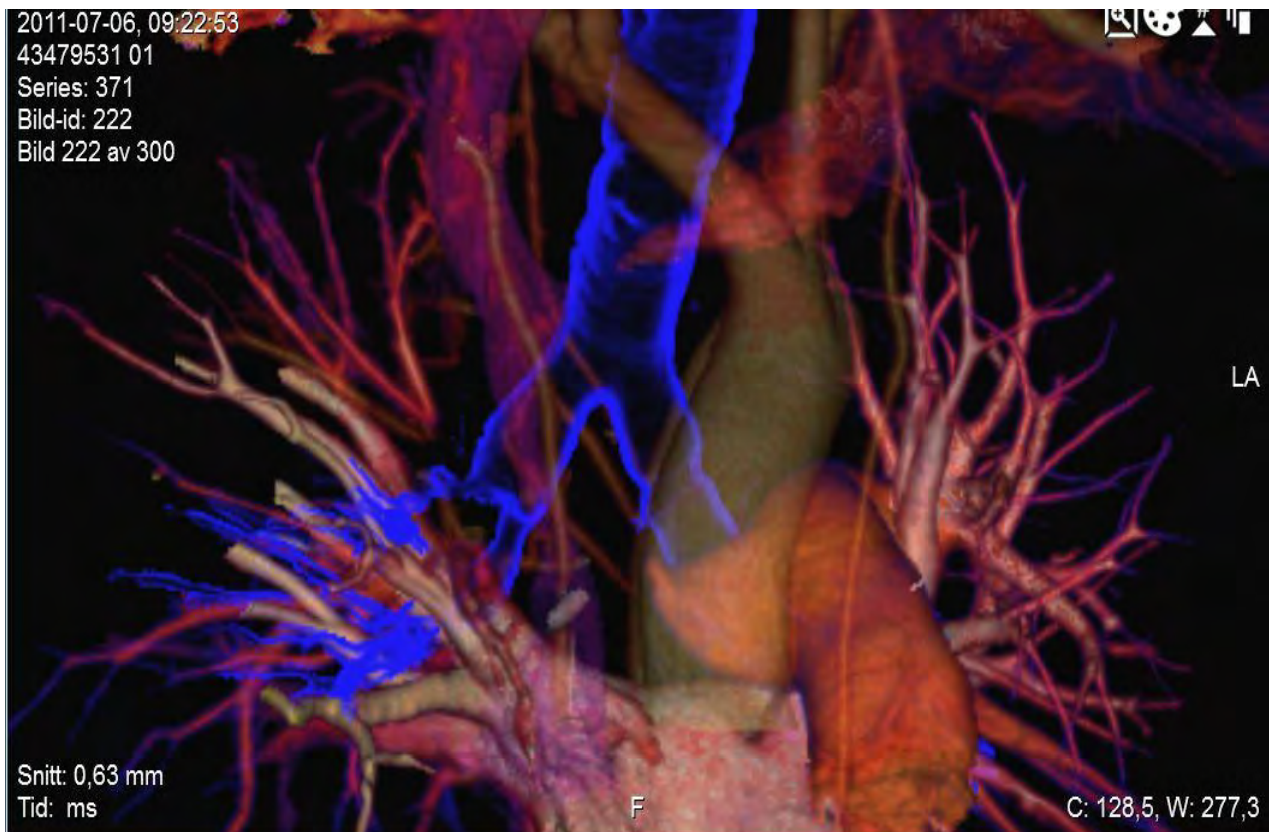


Figure 1b. CT examination 2011-07-06. Enlargement of figure 1a to be compared with figure 2C in the article.

This raises the suspicion that Drs. Jungebluth and Macchiarini have chosen to use an image taken only 4 weeks after implantation and claimed that it demonstrates "an almost normal airway" at 5 months after implantation of the synthetic trachea.

If this is confirmed then this can only be interpreted as scientific misconduct and falsification of data. To suggest that the time of examination has been accidentally misrepresented is not plausible since this was the only examination using the VR technique that was performed *after* the implantation surgery and *before* final submission of the article to *The Lancet*.

Furthermore, inspection of the radiological examination performed on 2011-07-06 that Drs. Jungebluth and Macchiarini seem to have used as a 5-month follow up image does not show findings that by any definition can be considered as "an almost normal airway". All images from that examination demonstrate severe airway pathology consisting of constriction, fistulation, and air surrounding the synthetic implant already 27 days after implantation.

In the series of figures below (figures 2a-b, 3a-c, 4) only signs of severe pathology secondary to or directly in contact with the synthetic implant are pointed out. Each picture is only a single frame of the radiological exam showing the pathological features from different perspectives proving irrefutably that this is not an "almost normal" airway.

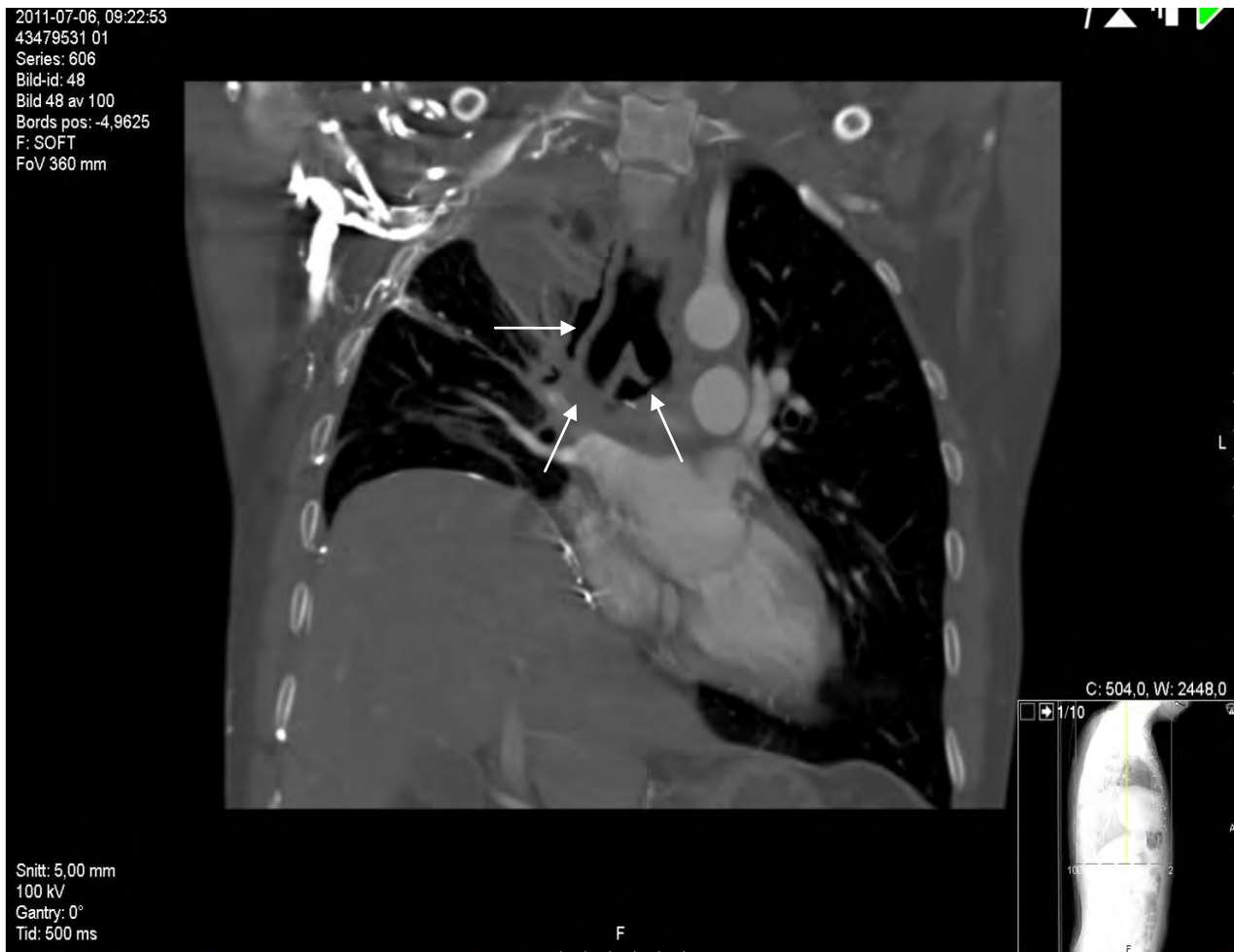


Figure 2a. CT examination 2011-07-06, 27 days after implant of synthetic trachea. Frontal view. Arrows from left to right: air outside the synthetic scaffold, constriction of the right distal anastomosis (connection) between synthetic trachea and native right main bronchus opening, fistula at the site of the distal synthetic tracheas "left leg" and the patient's left main bronchus anastomosis.

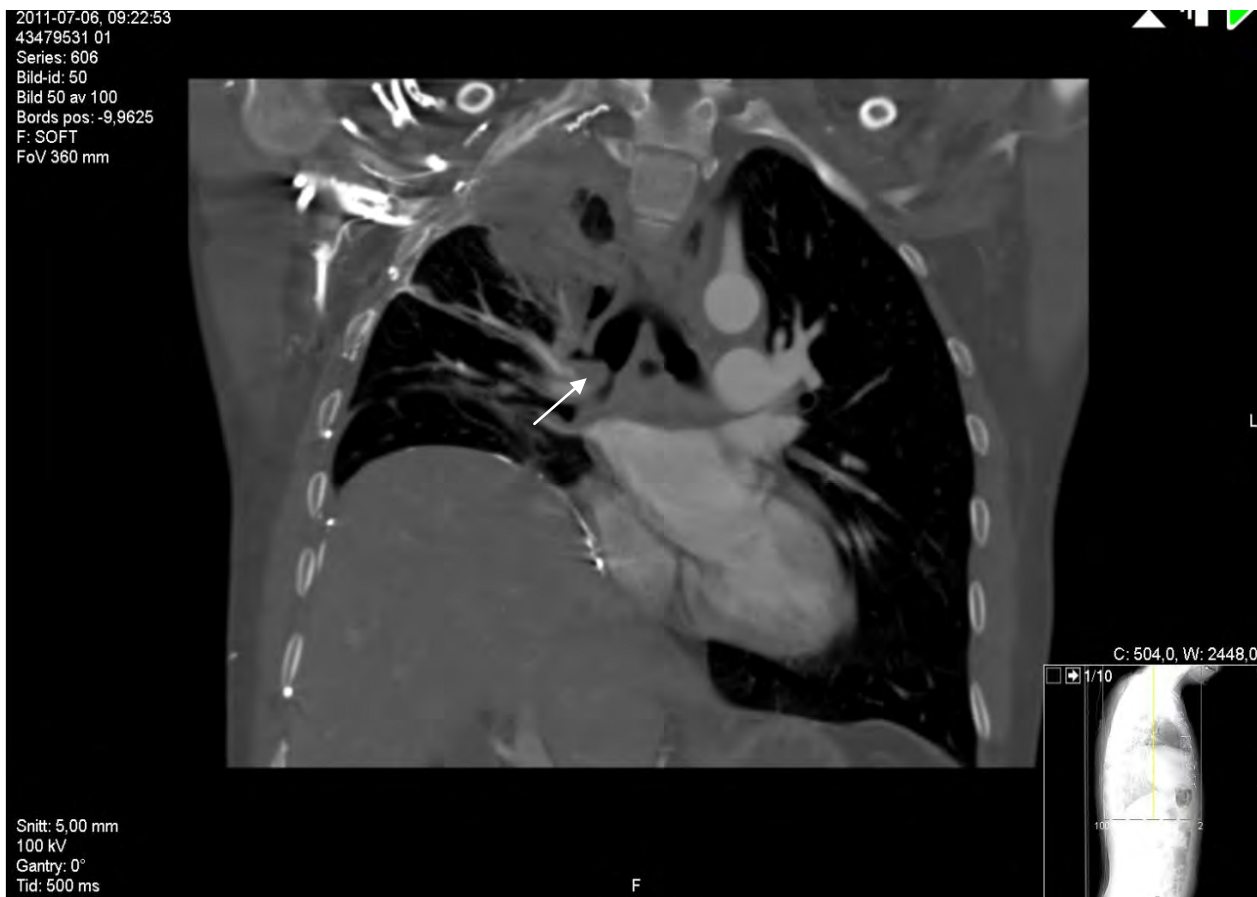


Figure 2b. CT examination 2011-07-06, 27 days after implant of synthetic trachea. Frontal view. Arrow: constriction of the right distal anastomosis between synthetic trachea and native right main bronchus opening.



Figure 3a. CT examination 2011-07-06, 27 days after implantation. Transversal view. Arrows from right to left: start of right main bronchus constriction (compare to figures 3b,c showing increasing constriction in more distal images from the chest), air outside the synthetic scaffold, large fistula at the site of the distal left main bronchus anastomosis.



Figure 3b. CT examination 2011-07-06, 27 days after implantation. Transversal view. Arrows from left to right: increased constriction of the distal right anastomosis (compared to figure 3a), air outside the synthetic scaffold, large fistula at the site of the distal left main bronchus anastomosis.

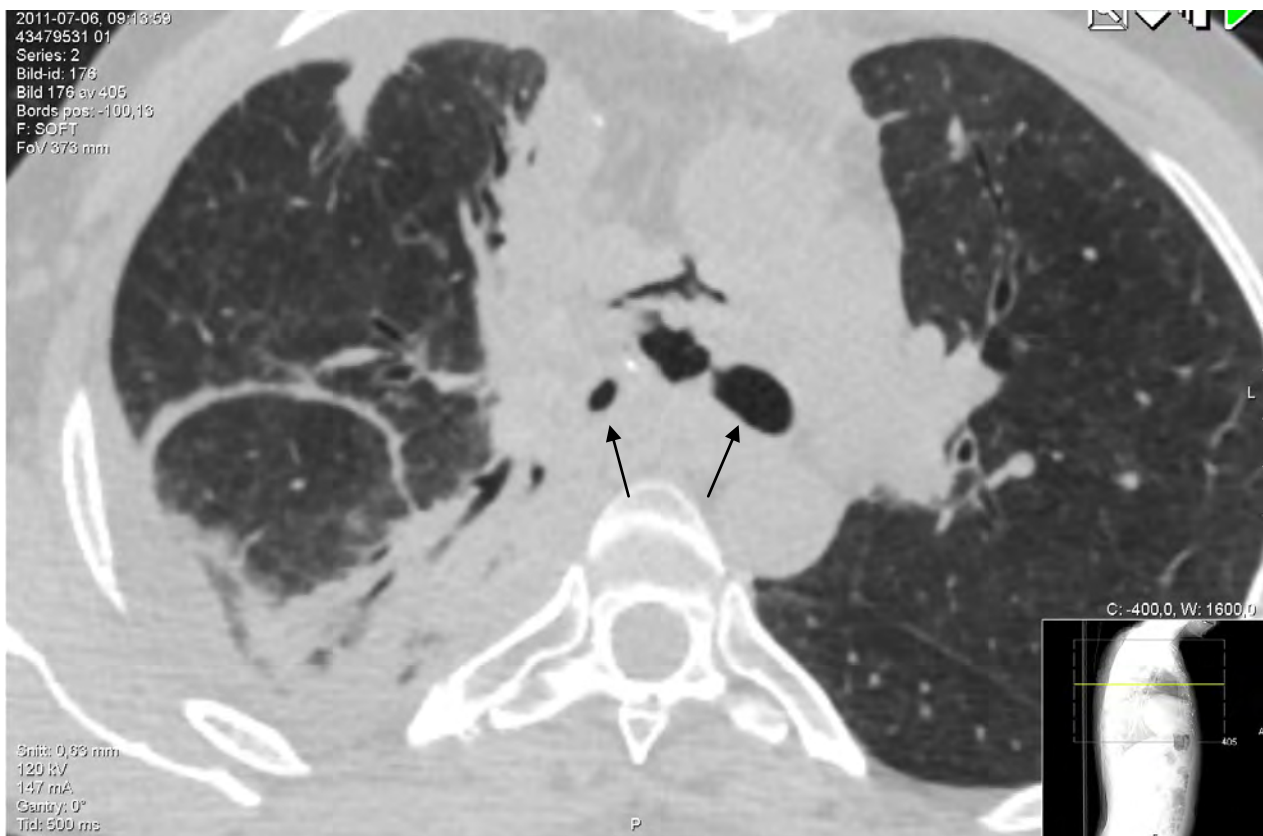


Figure 3c. CT examination 2011-07-06, 27 days after implantation. Transversal view. Arrows from left to right: increased constriction of the distal right anastomosis/right main bronchus opening (compare to figures 3a,b) compare to left main bronchus (right arrow).

Furthermore, in the figure legend to figure 2C in the article, the authors states that the blue colored image shows "Air in airways is shown in bright blue". In the radiological examination from the very same date, 2011-07-06, from which the figure 2C in the article seems to be taken, the blue colored volume rendered image can be individually analyzed as it is independently saved in the archive.

Even if all the tissues and implant are removed, the image cannot be depicted as showing evidence of "an almost normal airway" as it verifies a pathologically constricted right main bronchus 27 days after implantation.



Figure 4. CT examination (volume rendered image) 2011-07-06, 27 days after implantation showing only the air in the airway (the same blue "tube" as in the articles' figure 2C but without synthetic implant and surrounding tissues). Arrow significant constriction of the distal right anastomosis between synthetic trachea and native right main bronchus.

The severe constriction of the right main bronchus anastomosis, the lack of normal respiratory epithelium (figure 5a) and fistulation at the site of left main bronchus anastomosis (figure 5b) was verified by bronchoscopic examination on 2011-08-16, 10 weeks after implantation (2011-06-09).

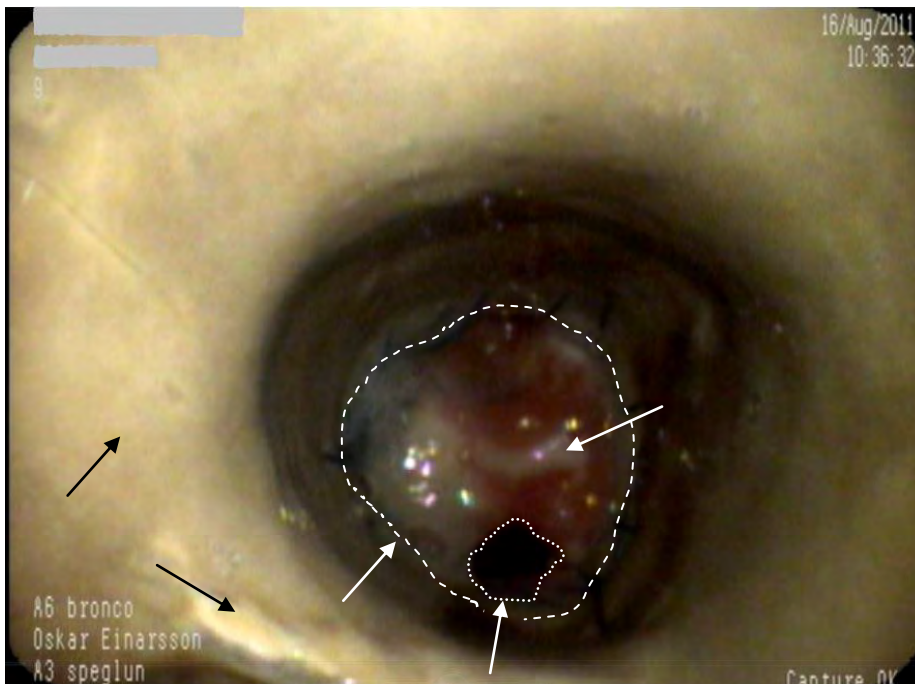


Figure 5a. Bronchoscopy 2011-08-16, 10 weeks after implantation (performed on Island). Distal right main bronchus anastomosis (the synthetic tracheas "right leg"). Arrows from left to right: nude wall of the synthetic trachea without any signs of epithelium (tissue layer), synthetic carina (separating ridge between the synthetic right and left main bronchuses), large dotted line: distal right anastomosis, small dotted line: obstructed native right main bronchus opening (should have had the same area as the large dotted line) blocking the right lung from normal ventilation due to extensive granulation (inflammatory) tissue.

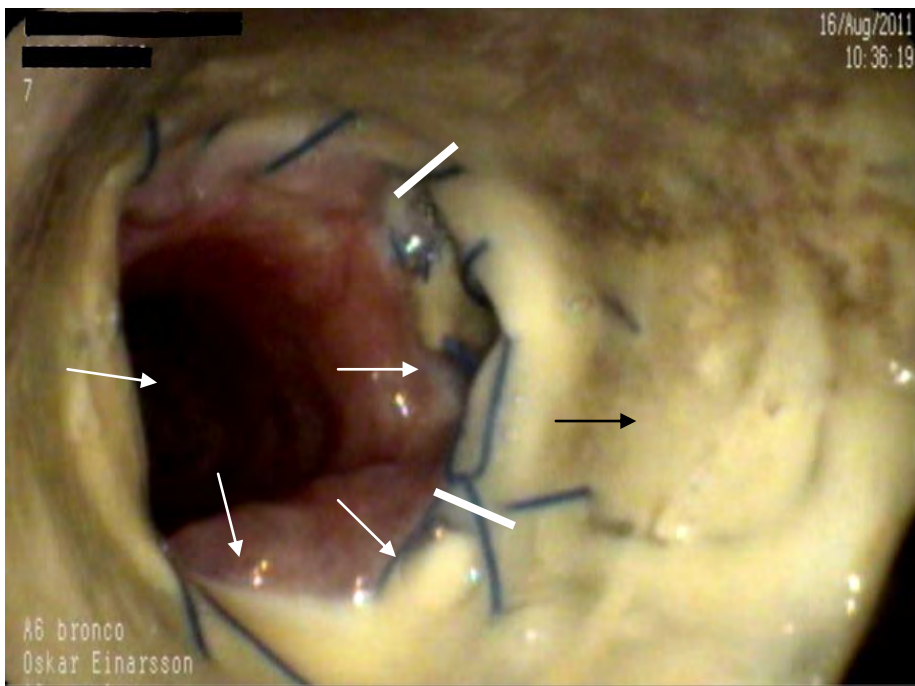


Figure 5b. Bronchoscopy 2011-08-16, 10 weeks after implantation. Distal left main bronchus anastomosis (the synthetic tracheas "left leg"). Arrows from left to right: left main bronchus opening, granulation tissue, nude (blue) sutures, thick white lines marks fistula opening (covering ca. 20% of the anastomotic circumference), nude wall of the synthetic trachea with no signs of regenerated airway or other epithelium.

Bronchoscopic examination from 2011-11-21, 5½ months after implantation, verifies the presence of a severely pathological airway without signs of regenerated trachea, normal respiratory, or any other epithelium on the synthetic tracheas surface.

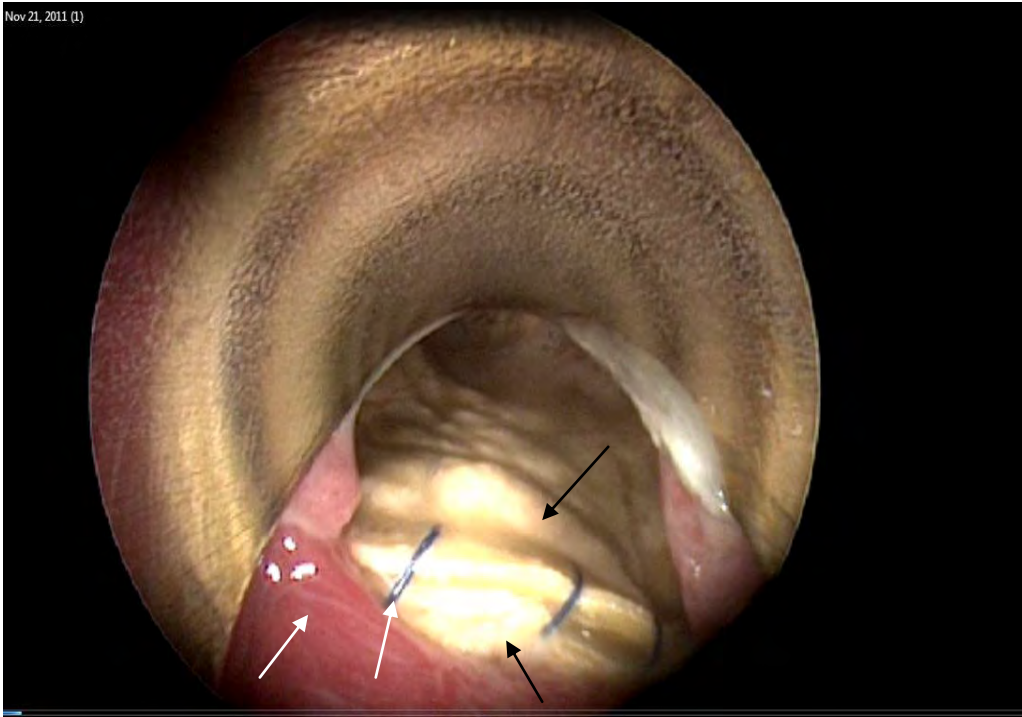


Figure 6a. Bronchoscopy 2011-11-21, 5½ months after implantation. Arrows from left to right: granulomatous (inflammatory) tissue, nude (blue) sutures, proximal (upper) connection between native trachea (reddish tissue) and nude synthetic implant (white-yellowish) without any covering airway tissue or epithelium.

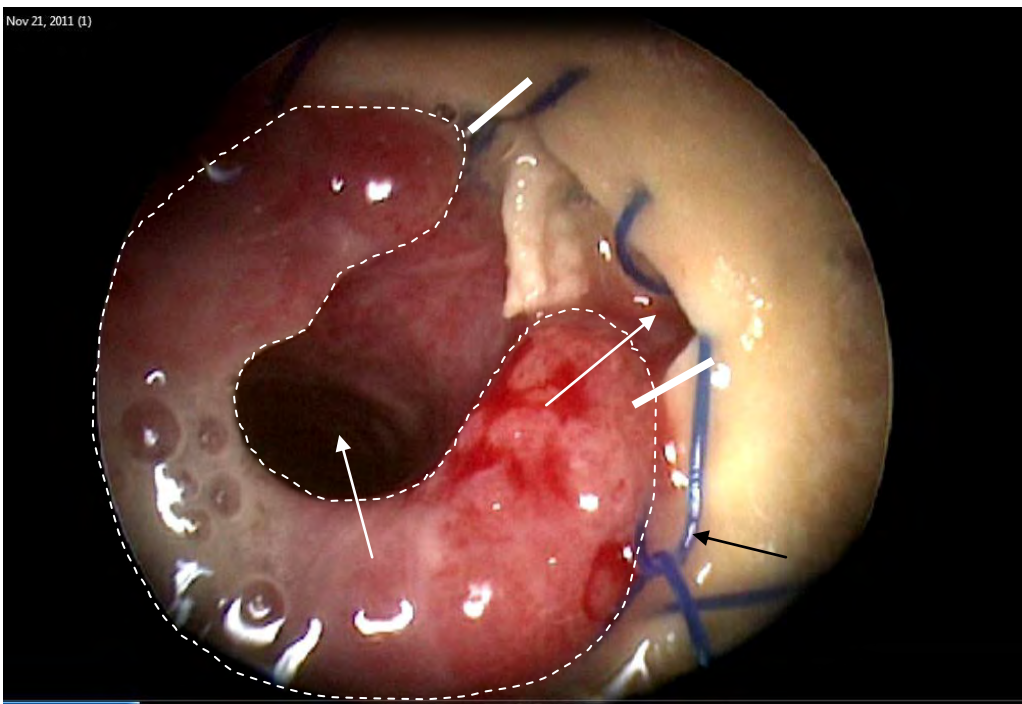


Figure 6b. Bronchoscopy 2011-11-21, 5½ months after implantation. Dotted line: area of excessive granuloma formation (inflammatory tissue) obstructing the left main bronchus opening. Arrows from left to right: native left main bronchus opening, thick white lines marks fistula opening in distal left main bronchus anastomosis (covering ca. 20% of the anastomotic circumference), nude (blue) sutures.

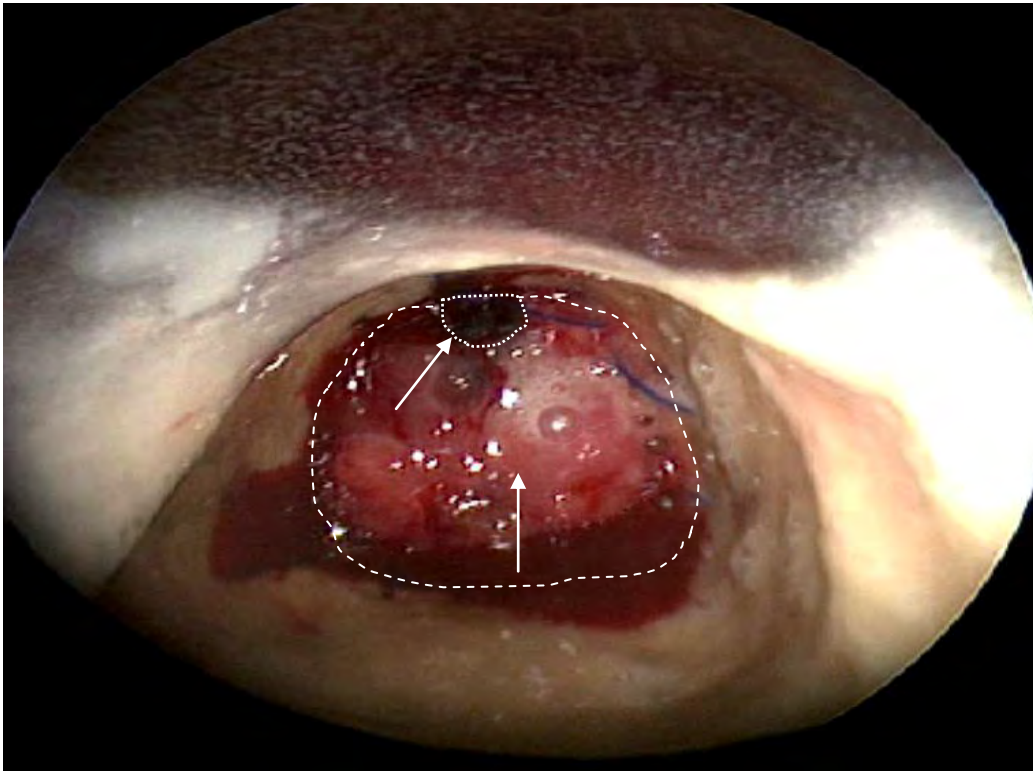


Figure 6c. Bronchoscopy 2011-11-21. Arrows from left to right: complete obstruction of native right main bronchus opening, large dotted line marks the distal right anastomosis, small dotted line marks the obstructed native right main bronchus opening (which should have had the same area as the large dotted line) blocking the right lung from normal ventilation, excessive granulation (inflammatory) tissue blocking the main bronchus lumen, nude synthetic trachea without any signs of normal airway tissue.

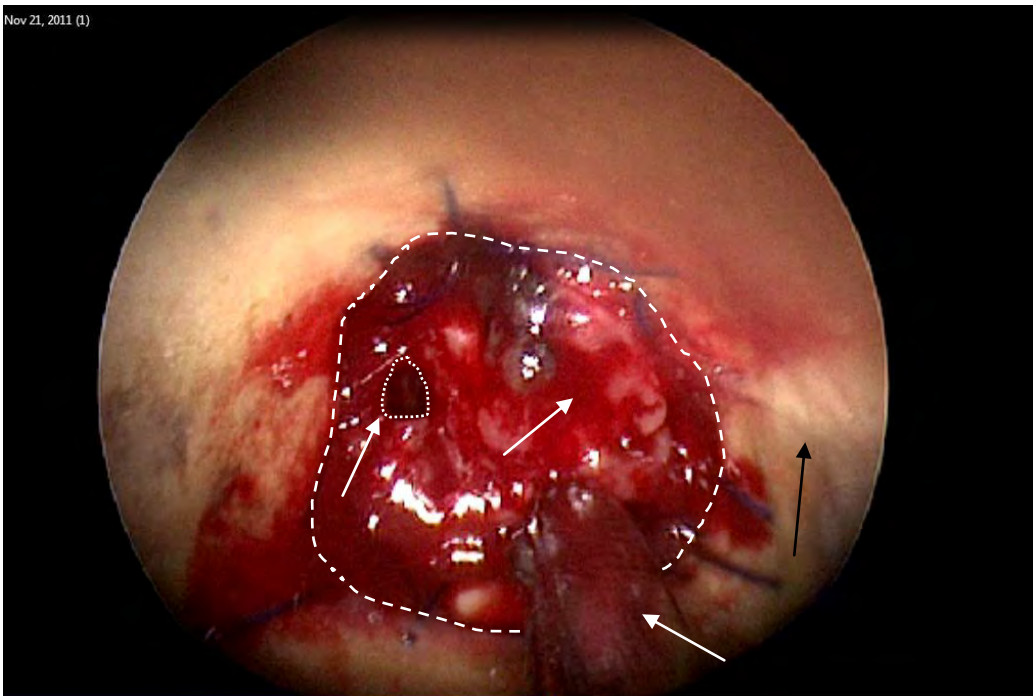


Figure 6d. Bronchoscopy 2011-11-21. Arrows from left to right: complete obstruction of native right main bronchus opening, large dotted line marks the distal right anastomosis, small dotted line marks the obstructed native right main bronchus opening (which should have had the same area as the large dotted line) blocking the right lung from normal ventilation, excessive granulation (inflammatory) tissue blocking the main bronchus lumen, surgical instrument to remove obstructing granulation tissue, nude synthetic trachea without any signs of normal airway tissue.

Radiological examination performed on 2011-11-22 (Figures 6a-c, 7), 5½ months after implantation 2011-06-09, verifies bronchoscopic findings of severe airway pathology consisting of bilateral fistulations, obstruction of airway and air surrounding the implant. Stents have been placed in an attempt to obliterate fistulation. The presence of fistulation is indicative of chronic infection and inability of the synthetic implant to heal into the surrounding native tissue, as is the continuous ingrowth of obstructive granulomatous tissue (threatening ventilation) is indicative of chronic inflammation.

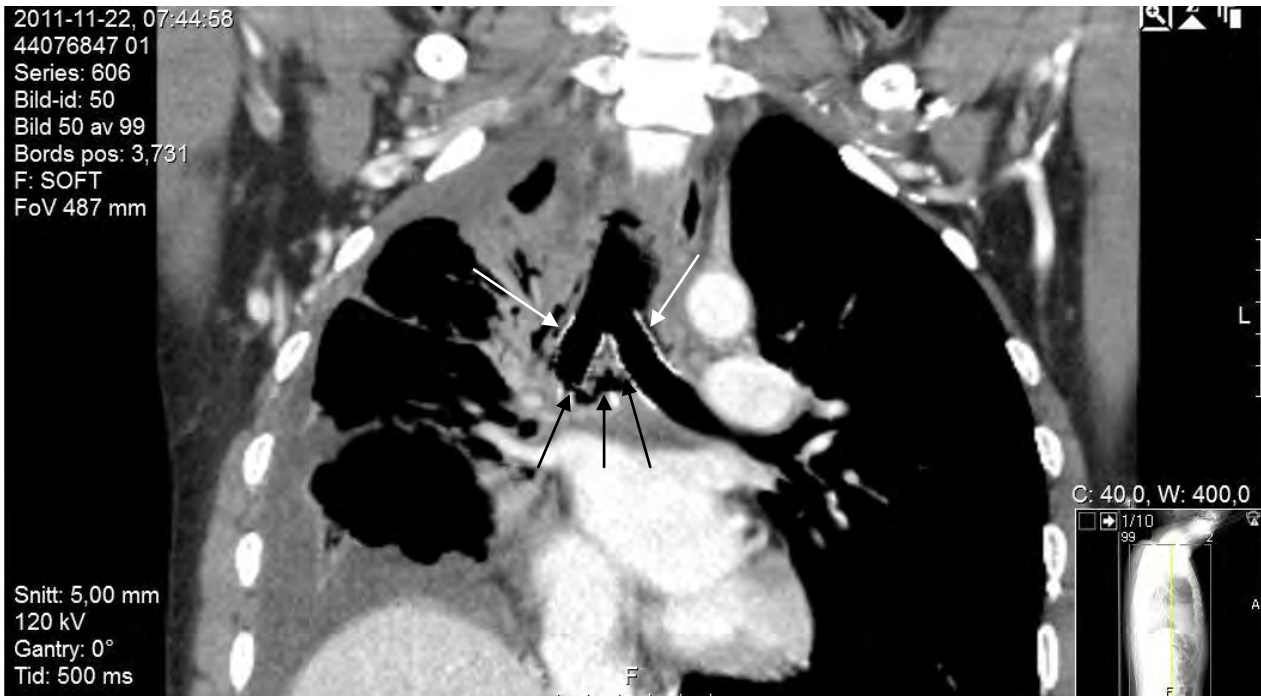


Figure 6a. CT examination 2011-11-22, 5½ months after implantation. Arrows from left to right: stent in the right main bronchus, fistula at the distal right main bronchus anastomosis, air outside the synthetic scaffold, fistula at the distal left main bronchus anastomosis, stent in the left main bronchus.



Figure 6b. CT examination 2011-11-22, 5½ months after implantation. Frontal view. Arrows from left to right: stent in the right main bronchus, circumferential fistula at the distal right main bronchus anastomosis (black double arrow), fistula at the distal left main bronchus anastomosis, stent in the left main bronchus.

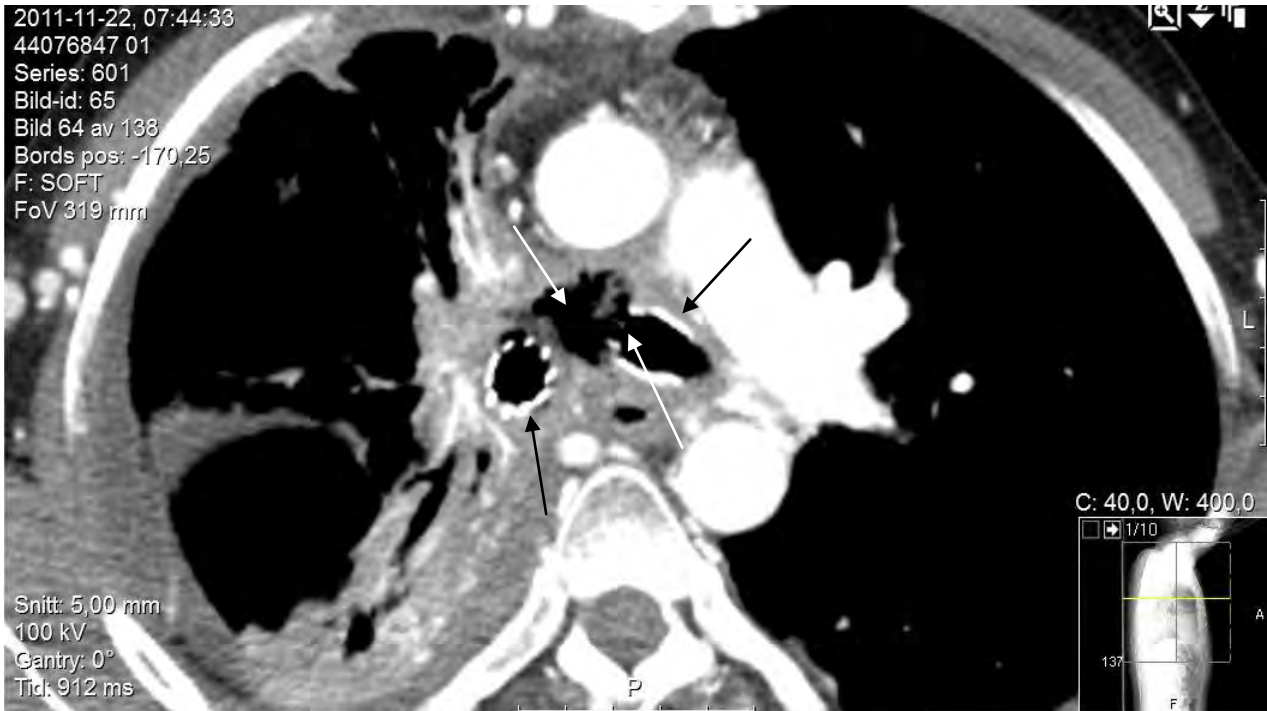


Figure 6c. CT examination 2011-11-22, 5½ months after implantation. Transversal view. Arrows from left to right: stent in the right main bronchus, air outside the synthetic scaffold, large fistula at the distal left main bronchus anastomosis, stent in the left main bronchus,

The 3rd radiological examination showing 3-D volume rendered images was performed on 2011-11-22, 5½ months *after* stent implantation on the day before (2011-11-21) due to severe airway pathology (obstruction, bilateral fistulations between synthetic trachea and left and right bronchi).

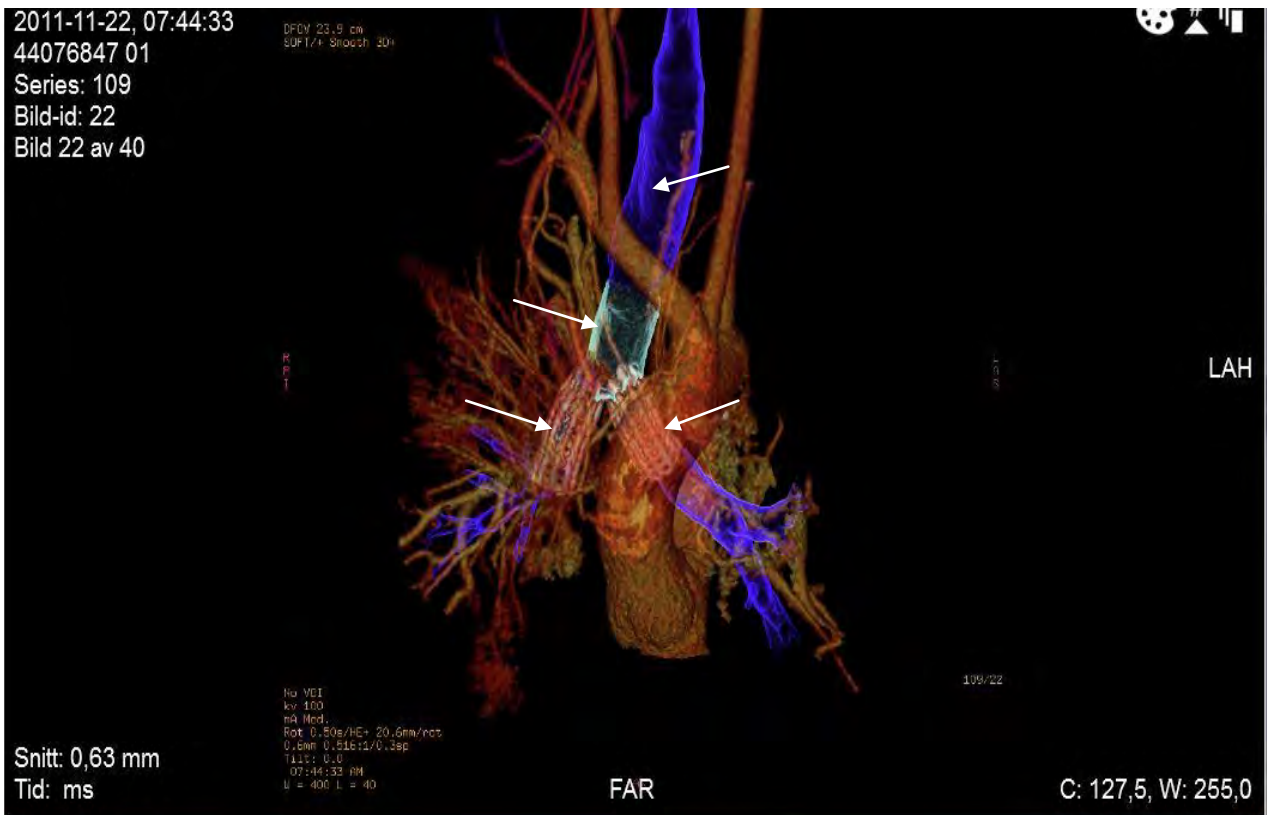


Figure 7. CT examination (VR image) 2011-11-22, 5½ months after implantation. Frontal view. Arrows from left to right: stent in the right main bronchus, synthetic trachea, tracheal “blue air tube”, stent in the left main bronchus.

Three imaging examinations have been presented above; 2011-07-06 (CT-VR), 2011-08-16 (filmed bronchoscopy) and 2011-11-22 (CT-VR), which clearly and in detail demonstrates the patient's airway at 4 weeks, at 10 weeks and at 5½ months after implantation. All three examinations demonstrate serious airway pathology and can be regarded as three individual time checkpoints.

Drs. Jungebluth and Macchiarini may postulate that the airway was "*almost normal*" at 5 months, which would imply that severe pathology which evidently was present at 4 and 10 weeks would have developed into "*almost normal*" at 5 months (when the final proofs were admitted to the Lancet) despite any imaging evidence for such a statement and then, after another 2 weeks (at 5½ months) the airway apparently degenerated into its severely pathological state as demonstrated above. This is not just plain absurd, it is of course impossible and an obvious example of gross misrepresentation. Unless proven otherwise, this is in itself sufficient to warrant retraction of the article, independent of the exhausting evidence we have already provided.

In conclusion, we appeal to Karolinska Institutet to investigate this new evidence of scientific misconduct. Drs. Jungebluth and Macchiarini have in all likelihood changed the dates of the radiological exam and neglected to divulge the evidence of pathology seen in the original radiological and bronchoscopic examinations.

More than two years have now transpired since we first reported evidence of serial scientific misconduct on the part of Dr. Macchiarini. This publication, along with a number of previously reported papers are allowed to persist in the medical literature despite that an insurmountable body of evidence demonstrating falsification, omission or beautification of data has been provided by us and the external investigation (1, 7). The continued inability of Karolinska Institutet to act accordingly and retract this article is a testimony to the moral paralysis afflicting this institution and is an insult to the patients and their relatives who have been victimized by its ineptitude.

With concern

Matthias Corbascio, MD, PhD, Assoc Prof

Thomas Fux, MD

Department of Cardiothoracic Surgery and Anesthesiology
Karolinska University Hospital, Solna
SE-171 76 Stockholm
Sweden

Karl-Henrik Grinnemo, MD, PhD, Assoc Prof

Oscar Simonson MD, PhD

Department of Cardiothoracic Surgery
Uppsala University Hospital
SE-751 85 Uppsala
Sweden

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2. Three-dimensional volume rendering of spiral CT data: theory and method. Calhoun PS, Kuszyk BS, Heath DG, Carley JC, Fishman EK. *Radiographics*. 1999 May-Jun;19(3):745-64
3. Interactive three-dimensional volume rendering of spiral CT data: current applications in the thorax. Johnson PT, Fishman EK, Duckwall JR, Calhoun PS, Heath DG. *Radiographics*. 1998 Jan-Feb;18(1):165-87. Review.
4. Decision by Vice-Chancellor Anders Hamsten 2015-08-28 (Dnr 2-2184/2014), Comment on the statement of opinion by Bertil Leidner, 2015-06-24, page 2 “*Concerning the responsibility for my co-authorship.*”
5. Respond by Dr Paolo Macchiarini to the Vice-Chancellor Anders Hamsten 2015-06-26, Re: Statement of opinion on assignment ref. 2-2184/2014, Appendix 7, Time Line Table, page 20.
6. Respond by Dr Philipp Jungebluth to the Vice-Chancellor Anders Hamsten 2015-06-24, Re: Statement of opinion on assignment ref. 2-2184/2014, page 8.
7. Prof Gerdin’s final report “*Statement of opinion on assignment ref. 2-2184/2014*”, May 13, 2015.