Abstract

Primary blast lung injury frequently complicates military conflict and terrorist attacks on civilian populations. The fact that it occurs in areas of conflict, or unpredictable mass casualty events makes clinical study in human casualties implausible. Research in this field is therefore reliant on the use of some form of biological or non-biological surrogate model. We briefly review the modelling work undertaken in this field to date and describe the rationale behind the generation of our *in-silico* physiological model.

Introduction

First described by Hooker in 1924(1) as a “single gross lesion found post mortem after exposure to air concussion due to high-explosive”, primary blast lung injury (PBLI) is currently defined as “radiological and clinical evidence of acute lung injury occurring within 12 hours of exposure and not due to secondary or tertiary injury”.(2) It is a disease characterized by intra-parenchymal haemorrhage, laceration and pneumothoraces.(3) In the absence of a specific biomarker or radiological hallmark, it can be difficult to distinguish PBLI with confidence from other forms of lung damage in complex patterns of injury. PBLI occurred in some 7% of UK casualties in the most recent conflict in Afghanistan despite the rudimentary nature of the opposition forces.(4) It is likely that PBLI will be an increasingly encountered by UK Defence Medical Services (DMS) in future more industrialised conflicts due to a combination of factors. Firstly, a more economically capable opponent will be equipped with the wide variety of thermobaric weaponry that is readily available and has been recently used in the Balkan and Chechnian conflicts.(5) Secondly, British military casualties exposed to such weapons are more likely to survive to reach hospital as improvements in personal protective equipment (6) and pre-hospital care reduces immediate fatalities due to penetrating injury.(7) There is thus a need to increase our understanding of the pathophysiology of this disease and to create accurate research models of PBLI.

Modelling based research

Modelling is the use of a surrogate entity to represent a complex system in a readily reproducible manner. Models can be either biological or non-biological. Biological models are further subdivided into in-vitro (cell culture), ex-vivo (live organ) or in-vivo (live animal).(8) Non-biological models are either computational (*"in-silico"*) or physical (Anthropomorphic) surrogates of the biological system of interest.

As a research technique, the validity of modelling parallels that of clinical trials or laboratory study.(9) Non-biological based research is cheaper than animal modelling, requires less stringent ethical approval and can accommodate scenarios that are unachievable in live animal or human research (such as multiple casualty with multiple injury events). It can do this in an easily repeatable manner so that adequately powered studies which can achieve statistical significance can be undertaken. Modelling also facilitates the Ministry of Defence's ambition of limiting animal experimentation (10) and the impetus for the scientific community to "*Replace, Reduce and Refine"* when considering the use of live animals in research.(11, 12)

Both biological and non-biological models of primary blast injury to the chest exist and are in use. The original biological PBLI modelling work of note was undertaken by Bowen and colleagues in 1968.(13) This frequently referenced work is still used as a benchmark comparator by subsequent researchers despite significant weaknesses. Limitations include its use of a broad range of large and small animal species, the mixing of long and short duration blasts and the mixing of blast over-pressure measuring modalities (reflected and incident measurements differ significantly for any given explosion introducing significant differences in recorded over-pressure). This work suggests exposure injury and lethality thresholds, but having been undertaken almost 50 years ago does not reflect the significant advances in medical care achieved over this period. It also does not describe the severity of injury in survivors and the likely requirement for, and duration of, intensive care management. Blast injury

research continues using both in-vivo and *ex-vivo* biological models.(14-16) Rodents are commonly used to model lung injury due to a variety of mechanisms including blast. (17) and human cadaveric specimens have been used to examine the effects of under-vehicle explosions on the lower limb.(18)A more recent example of *in-vivo* blast research is the porcine work undertaken by Garner *et al* at the Defence Science and Technology Laboritories (DSTL) in Porton Down.(19) This work demonstrated a significant increase in mortality when haemorrhagic shock and blast exposure are combined which subsequently lead to a change in resuscitation protocol within the DMS. The four arms of this study was limited to six to eight subjects for the reasons discussed above and so could only accommodate the study of an immediately life threatening combination of injuries (i.e. course data) and not the intermediate term and more subtle outcomes normally sought in medical intervention research.

One of the earliest examples of anthropomorphic modeling in blast lung research was the Blast Test Device (BTD) developed by the US military. It consists of a chest shaped metal cylinder with 4 pressure gauges, one on each wall of the chest. This simple device allowed the reliable measurement of blast loading even in complex scenarios such as a confined space.(20) The Swedish Defence Research Institute subsequently developed a more complex chest surrogate (the Swedish Dummy Torso, Figure. 1) aiming to produce a more biofidelic model. This model was constructed from a combination of strengthened rubber and foam with acoustic transmission facilitated through the use of water compartments. This model was able to match the human chest in terms of compressibility and natural frequency.(21) All such models facilitate the measurement of physical blast loading in any given scenario but do not inform as to the physiological consequences of such loading.

Computational modelling has evolved in parallel to advances in computing power. Finite element modeling (FEM) treats the subject of interest as a 3-dimensional mesh of finite blocks each of which has known mechanical properties. These individual components effect change on neighboring units in a predictable manner and thus physical effects on the subject as a whole can be predicted. A FEM model was commissioned by the UK coroner's office after the suicide bombings on the London transport network in 2005.(22) This quick-running model looked both at primary and secondary (fragmentation) injury resulting from detonation of an explosive device in a crowded area. It was able to generate an abbreviated injury score (AIS) for casualties based on blast injury threshold limits and likely fragmentation injury and so represents a significant step towards arming civil authorities and clinicians with clinically useful information. Whilst much faster than most FEM models, this model still requires 5 hours of run time to recreate 30 minutes of simulated time.(23) A FEM model of PBLI in sheep has recently been developed which can accurately predict the volume of injured lung following a blast but remains unable to inform the medical community regarding the likely level of care such casualties would need and it does not facilitate the study of potential medical interventions.(24) FEM modelling however normally takes several days per scenario and requires computing power that is not widely available. Despite advances in computer technology, FEM remains predominantly a tool to study structural rather than physiological consequences of injury.

Our current model

Our model is a modification of an existing *in-silico* cardio-respiratory simulator developed by Nottingham University.(25, 26) The Nottingham Physiological Simulator (NPS) models the cardiorespiratory components of the human body via mathematical equations using the Matlab software package (The Mathworks Inc, Natick, MA, USA). The model assumes that a patient is mechanically ventilated and not contributing to respiratory effort. Both the cardiovascular and respiratory systems are divided into a

series of individual components, each of which are described by a set of independent variables (Fig 2). At the beginning of a modelling study, these variables are initially set so that they represent the patient population to be studied. Once initiated, the model undertakes a series of pre-determined physiological equations for a period of 30 milliseconds which represents one physiological time slice *t.* The end product of this series of equations then determines the value of the variables used in the next time slice. This iterative process continues for the study run-time *T.*

The respiratory element of the model consists of the mechanical ventilator and breathing circuit, physiological deadspace (60 mL), anatomical and alveolar shunts and a variable number of ventilated alveoli each of which has its own vascular component. Inhaled gases consist of oxygen, nitrogen, carbon dioxide, water vapour and gas α (anaesthetic or toxic gases). The cardiovascular element is composed of 19 compartments each of which are described by both fixed parameters (unstressed volume and elastance coefficients, resistance and viscosity) and iteratively updated variables (pressure, flow and volume). The systolic/diastolic cycling is modelled through a repeating pulsatile activation function of variable duration.

The numerical simulations of the integrated model provide results that agree with clinical data available in the published literature and the model has also been validated in a number of earlier studies.(27)

Adapting the model to reflect PBLI within the military context

In order to adapt this model to reflect PBLI the known physiological responses to blast injury(28) were codified mathematically and applied to the model. This new model was then validated against the porcine cardiovascular and pulmonary data collected at the Defence Science and Technology Laboritories (DSTL).(19, 29) In this model terminally anaesthetised adult white pigs are exposed to a fixed sub-lethal blast dose and ventilation continued under anaesthesia for the duration of the trial period prior to

terminal anaesthesia.(30) Our model has produced results closely matching this *in-vivo* data for both blast and combined blast and haemorrhagic shock.

For the model to be of relevance to the DMS we feel that it needs to meet several criteria. Primarily, it must be validated against the human injury experienced by UK service personnel suffering PBLI in combat. To this end we are creating a clinical database of UK PBLI victims generated in the recent conflict in Afghanistan which will be used to inform the model as to blast-dose related physiological effect and outcome. We need to be able to utilise the model throughout the chain of care from the point of wounding to rehabilitation. It therefor needs to be able to accommodate the study of buddie-buddie care in a pre-hospital environment, potential medical interventions in a Role II/III emergency department and also a variety of ventilatory approaches whilst mechanically ventilated in intensive care. In order to achieve this several adaptions need to be made. It must be able to model spontaneous ventilation in the pre-hospital environment, the effect of possible modulators of pulmonary inflammation and biotrauma that could be administered both in the pre-hospital or emergency department and finally it should be able to replicate the consequences of intensive care management including ventilator induced lung injury (VILI), oxygen toxicity and a fluctuating fluid volume status. In addition to this we hope to make the software sensitive to the age and gender of the casualty.

Diagnostically we are concurrently developing computerised tomography (CT) criteria for identifying and quantifying PBLI. We are also in the early stages of attempting to identify potential mRNA based biomarkers for the disease. CT images consist of voxels (3-dimensional pixels), each of which can be interrogated for their density measured in Hounsfield units (HU). Existing Imaging software (Analyze®) allows 3-D reconstructions of CT lung images from PBLI casualties to be created which only displays voxels from poorly or non-aerated lung tissue (voxel range of -250 to +250 HU; Figure.3). This data can also be used to quantify the proportion of lung tissue that

is poorly or non-aerated as a consequence of PBLI (Figure. 4).(31) Early evidence suggests that this method may prove useful in the identification of casualties with PBLI.(32) This work will be used to inform our computerised model of the proportion of non-functioning alveoli in our human casualties in order to increase its fidelity and clinical range.

Future direction.

Despite this extensive modeling activity, it has not kept pace with advances in medicine such as physician lead pre-hospital care, highly orchestrated and effective emergency department management of critically injured casualties, intensive care therapy and computed tomography imaging. It also fails to recognize the fact that improved pre-hospital care will result in increasingly severe cases of PBLI requiring management by the DMS. No model or measurable parameter exists that will either inform clinicians of the degree of injury resulting from shockwave exposure alone, can predict the ongoing physiological compromise surviving casualties will suffer or allow clinicians to model different treatment, mitigating or preventative strategies.(33) It is the ambition of our group to create a militarily relevant blast lung injury model validated against human combat injury and augmented by specific serological and CT markers of disease severity that will facilitate future research in this field.

Conflict of Interest

No conflicts of interest declared.

References

1. Hooker DR. Physiological effects of air concussion. *American Journal of Physiology.* 1924;67(2):219-74.
2. I Mackenzie, Tunnicliffe B, J Clasper, P Mahoney, E Kirkman. What the intensive care doctor needs to know about blast-related lung injury. *Journal of the Intensive Care Society* 2013;14(4):303-12.
3. Wolf SJ, Bebarta VS, Bonnett CJ, Pons PT, Cantrill SV. Blast Injuries. *Lancet* 2009;374: 405-15.
4. Smith JE. The epidemiology of blast lung injury during recent military conflicts: a retrospective database review of cases presenting to deployed military hospitals, 2003-2009. *Philosophical transactions of the Royal Society of London Series B, Biological sciences* 2011;366(1562):291-4.
5 Dearden P. New Blast Weapons. J R Army Med Corps 2001;147: 80-86.
6 Breeze J, Lewis EA, Fryer R, Hepper AE, Mahoney PF, Clasper JC. Defining the essential anatomical coverage provided by military body armour against high energy projectiles. *J R Army Med Corps* 2016;162:284-290.
7 Davis PR, Rickards AC, Ollerton JE. Determining the composition and benefit of the pre-hospital medical response team in the conflict setting. *J R Army Med Corps* 2007;153: 269-273.
8. Cernak I.. Long-Term Effects of Blast Exposures. For the committee on the Gulf War and Health. Volume 9. Washington D.C.
9. Hardman JG, Ross JJ. Modelling: a core technique in anaesthesia and critical care research. *British Journal of Anaesthesia* 2006;97(5):589-92.
10. . wwwgovuk/guidance/research-and-testing-using-animals.
11. Russell WMS, Burch RL. The Principles of Humane Experimental Technique. Wheathampsted: Universities Federation for Animal Welfare; 1992.
12. The Animals Scientific Procedures Act (ASPA), (1986).
13. Bowen IG, Fletcher E, Richmond D. Estimate of Man's Tolerance to the Direct Effects of Blast. Technical progress report no. DASA-2113. In: Defence Do, editor. Washington DC: Defence Atomic Support Agency; 1968.
14. Breeze JCD, Mabbott A *et al*. Refrigeration and freezing of porcine tissue does not affect the retardadtion of fragment simulating projectiles.
15. Butler BJ, Bo C, Tucker AW *et al*. Mechanical and histiological characterisation of trachea tissue subjected to blast-type pressures. *Journal of Physics* 2014, Conference series 500.
16. Chai JK, Cai JH, Deng HP *et al.* Role of neutrophil elastase in lung injury induced by burn-blast combined injury in rats. *Journal of the International Society for Burn Injuries* 2013;39(4):745-53.
17. Brown RF, Cooper GJ, Maynard RL. The ultrastructure of rat lung following acute primary blast injury. *International journal of experimental pathology* 1993;74(2):151-62.
18. Masouros SD, NN, Ramasamy A *et al*. Design of a traumatic injury simulator for assessing lower limb response to high loading rates. *Annals of Biomedical Engineering* 2013;41(9):1957-67.

19. Garner J, Watts S, Parry C, Bird J, Cooper G, Kirkman E. Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage. *Ann Surg 2010;251: 1131-39*
20. Yu JH, Vasel EJ, Stuhmiller JH. Modeling of the Non-Auditory Response to Blast Over-pressure: Design and Field Test of a Blast Overpressure Test Module. Jaycor Inc; San Diego1990.
21. Jönsson A, Clemedson C, Arvebo E. An anthropomorpic dummy for blast research. Proceedings of the International Conference on Protective Clothing Systems 1981; August 23-27; Stockholm, Sweden.
22. Pope DJ. The development of a quick-running prediction tool for the assessment of human injury owing to terrorist attack within crowded metropolitan environments. Philosophical transactions of the Royal Society of London Series B, Biological sciences 2011;366:127-43.
23. Hepper AE, Pope DJ, Bishop M et al. Modelling the blast environment and relating this to clinical injury: experience from the 7/7 inquest. Journal of the Royal Army Medical Corps 2014;160:171-4.
24. Gibbons MM, Dang X, Adkins M, Powell B, Chan P. Finite Element Modeling of Blast Lung Injury in Sheep. J Biomech Eng 2015;137(4).
25. Hardman JG, Bedforth NM, Ahmed AB et al. A Physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation. Br J Anaesth 1998;81:327-32.
26. Hardman JG, Wills JS, Aitkinhead AR. Investigating hypoxaemia during apnea: validation of a set of physiological models. Anesth Analg 2000;90:614-8.
27. McCahon RA, Colomb MO, Mahajan RP, Hardman JG. Validation and application of a high-fidelity, computational model of acute respiratory distress syndrome to the examination of the indices of oxygenation at constant lung-state. British Journal of Anaesthesia 2008;101(3):358-65.
28. Guy RJ, Kirkman K, Watkins PE, Cooper GJ. Physiologic responses to primary blast. *The Journal of trauma* 1998;45:983-7.
29. Spear AM, Davies EM, Taylor C *et al*. Blast wave exposure to the extremities causes endothelial activation and damage. *Shock* 2015;44(5):470-8.
30. Garner JP, Parry C, Bird J, Kirkman E. Development of a large animal model for investigating resuscitation after blast exposure. *World J Surg* 2009;33:2194-202.
31. Heuer JF, Sauter P, Pelosi P *et al*. Effects of Pulmonary Acid Aspiration on the Lungs and Extra-Pulmonary Organs: A Randomised Study in Pigs. *Critical Care* 2012;16(2):R35.
32. Hulse EJ, Vliegenthart ADB, de Potter CMJ et al. Computed tomography voxel density and micro RNA analysis of blast lung injury. Poster Presentation, Military Health Services Research Society (MHSRS); 2016.
33. Panzer MB, Bass CR, Rafaels KA, Shridharani J, Capehart BP. Primary Blast Survival and Injury Risk Assessment for Repeated Blast Exposures. *Trauma Acute Care Surg* 2012;72(2):454-66.

Legends

Figure 1. Pictorial representation of the Swedish Dummy Torso.

Figure 2. Pictorial representation of our current *in-silico* PBLI model.

Figure 3. 3-D lung reconstruction. A significant proportion of the left (Red) lower lobe is not aerated in this PBLI casualty.

Figure 4. The histogram data from the 3D CT lung reconstruction denoting the distribution of voxels (y axis) and their densities in Hounsfield units (HU). Aerated lung exists between -1000 and -500 HU.

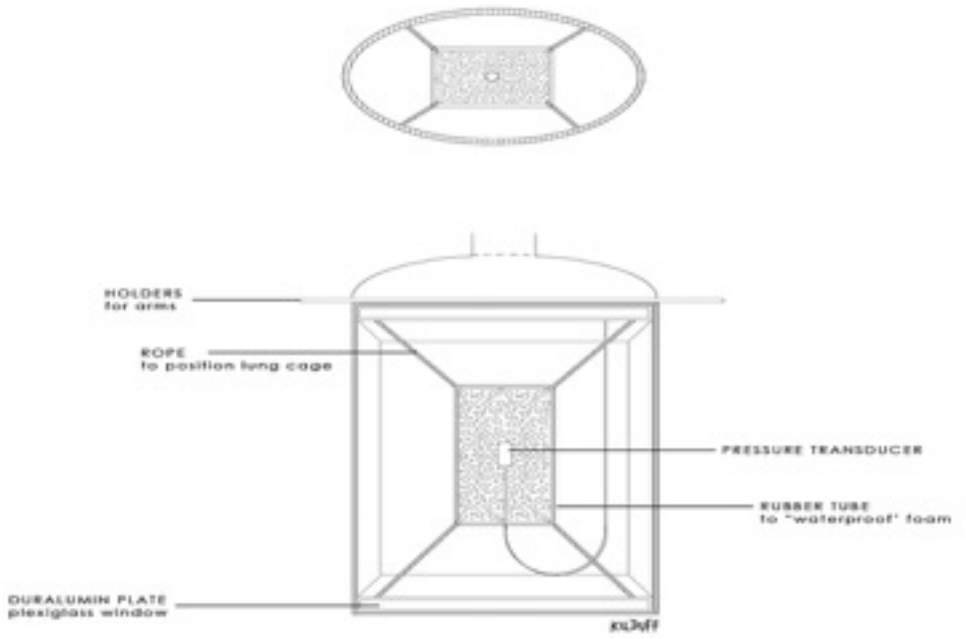
HOLDERS
for arms
ROPE
to position lung cage
PRESSURE TRANSDUCER
RUBBER TUBE
to "waterproof" foam
DURALUMIN PLATE
plexiglass window

Figure 1.

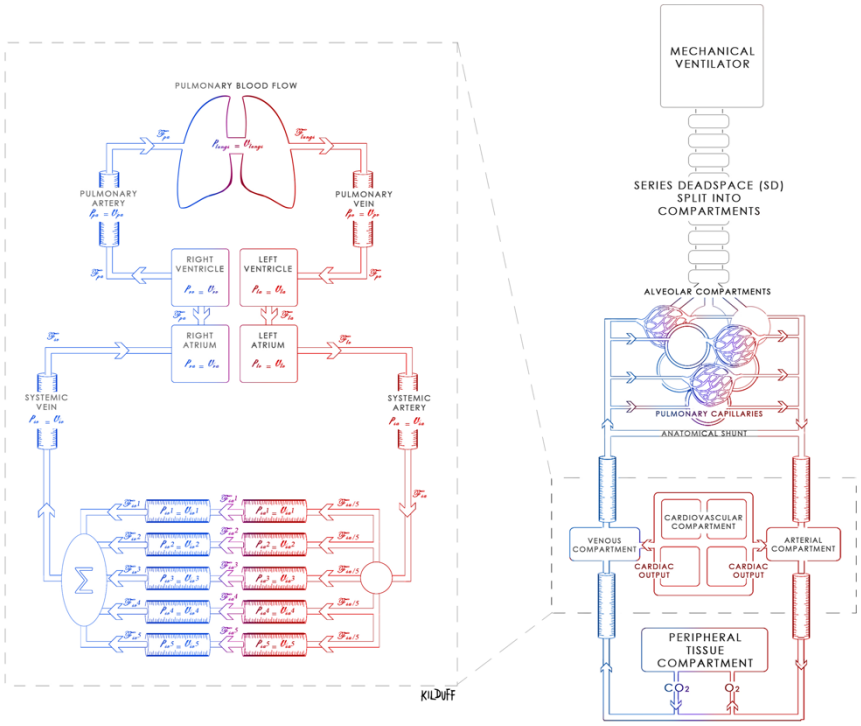
PULMONARY BLOOD FLOW
PULMONARY ARTERY
PULMONARY VEIN
RIGHT VENTRICLE
LEFT VENTRICLE
RIGHT ATRIUM
LEFT ATRIUM
SYSTEMIC VEIN
SYSTEMIC ARTERY
KILDUFF
MECHANICAL VENTILATOR
SERIES DEADSPACE (SD) SPLIT INTO COMPARTMENTS
ALVEOLAR COMPARTMENTS
PULMONARY CAPILLARIES
ANATOMICAL SHUNT
CARDIOVASCULAR COMPARTMENT
VENOUS COMPARTMENT
ARTERIAL COMPARTMENT
CARDIAC OUTPUT
CARDIAC OUTPUT
PERIPHERAL TISSUE COMPARTMENT
CO2
O2

Figure 2.

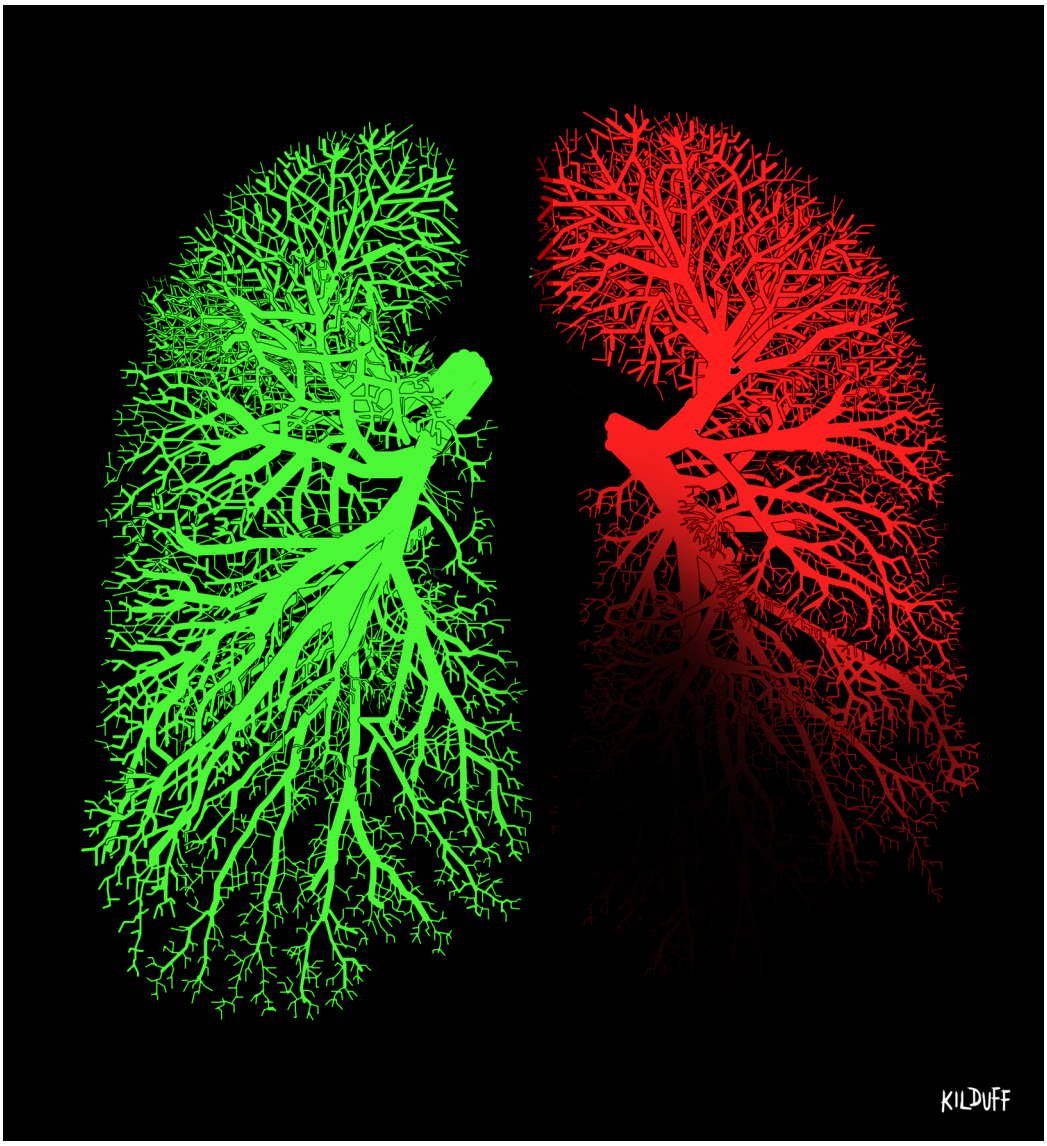

Figure 3.

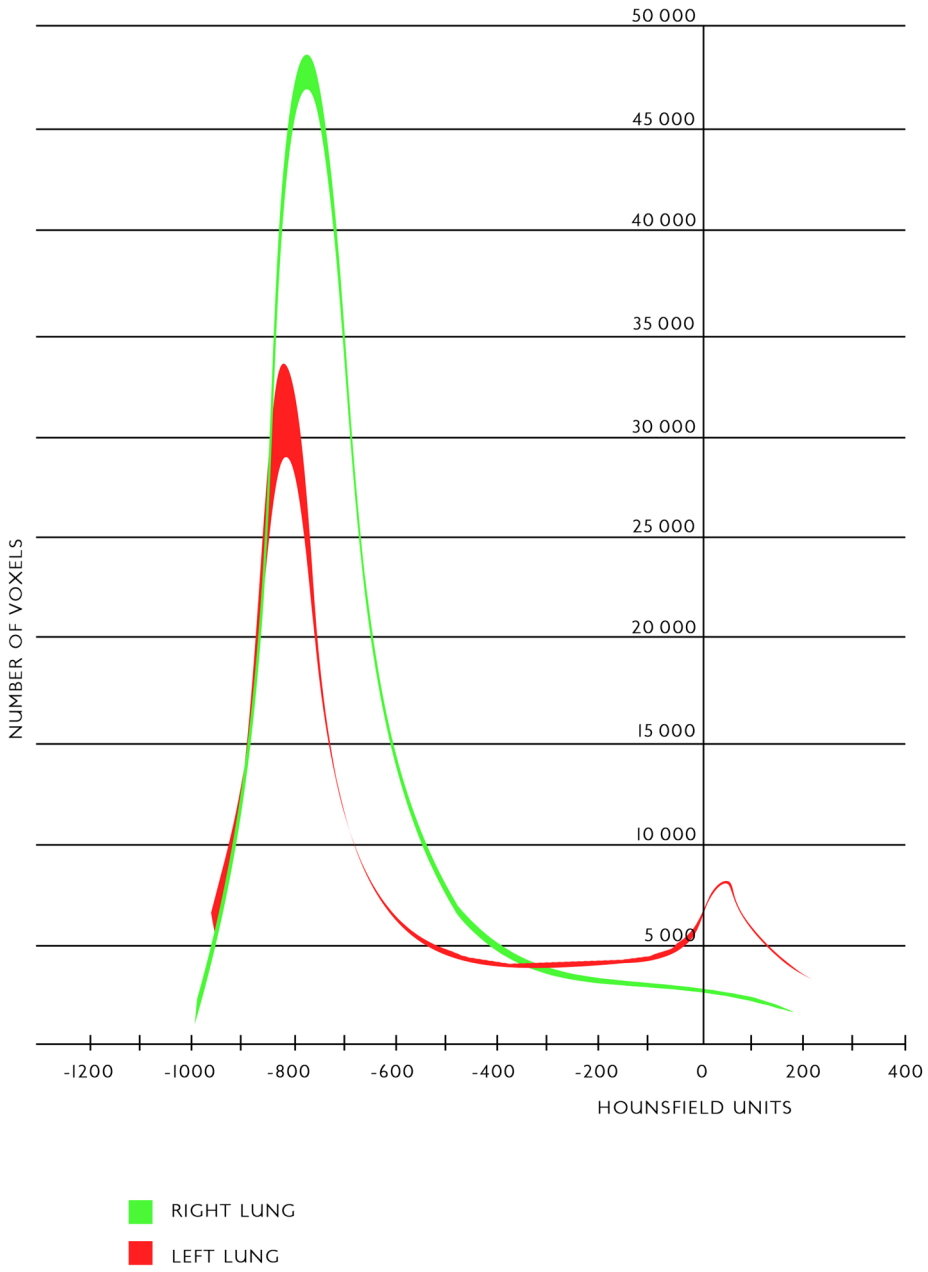
50 000
45 000
40 000
35 000
30 000
25 000
20 000
15 000
10 000
5 000
NUMBER OF VOXELS
-1200
-1000
-800
-600
-400
-200
0
200
400
HOUNSFIELD UNITS
RIGHT LUNG
LEFT LUNG

Figure 4.