On the innovative genius of Andreas Vesalius

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Chapter 8

Vesalius on respiration

Chapter based on article
Andreas Vesalius’ understanding of pulmonary ventilation
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Introduction
The historical evolution of the concepts regarding the chemical aspects of respiration has been amply documented [1], but relatively little has been written on the development of our understanding of the mechanical aspects of respiration [2]. The “father of physiology” Erasistratus (304 BC) accepted the diaphragm as the only muscle of breathing and Galen (ca.130-200) already recognized that the intercostal muscles and some accessory respiratory muscles are also involved [2]. Still, it was the anatomist Andreas Vesalius (1515 - 1564) who first recorded many of the mechanical details and structures of breathing that we currently know, in his epoch-making De Humani Corporis Fabrica Libri Septem (De Fabrica) [3].

So far, Vesalius’ records have received little attention because the anatomical illustrations rather than the text of De Fabrica got all attention in the majority of commentaries on this work [4-6]. Consequently, Vesalius’ understanding of negative intrapleural pressure was still ignored in 2002 [7]. In Vesalius’ time this may have been explained by the novelty of illustrating anatomical texts whereas [4], in our time, it may have resulted from difficulty of handling the Latin language [6, 8]. This excuse to disregard Vesalius’ text no longer prevails since the completion of an excellent English translation of the entire text of De Fabrica by the classicist Richardson and the anatomist Carman in 2009.

Vesalius’ instructions for a spectacular in vivo demonstration of pulmonary movements in a breathing dog inspired us to study de rest of De Fabrica to assess to what extent he understood the physiology of ventilation mechanics. In this chapter, we report on this assessment.

Materials and Methods
During normal tidal breathing, inspiration starts with contraction of the diaphragm and the external intercostal muscles to increase the size of the thorax. Subsequently, the negative pressure in the pleurae increases, the alveolar volume increases, and the intra-alveolar pressure decreases. The resulting gradient relative to atmospheric pressure causes air to enter the lungs. During this process pulmonary elastic recoil forces increase [9, 10]. Once the active inspiratory muscle contractions are stopped, these elastic recoil forces cause the intra-alveolar pressure to increase above atmospheric pressure and the lungs to partially collapse by expiration. Hence, normal tidal expiration is passive because no muscles need to contract to produce it. Accessory inspiratory muscles are brought into action for forced inspiration. Of these, the scalenus muscles are the first to start contracting and the sternocleidomastoid, trapezius and other muscles are gradually brought into action. Contraction of the abdominal (rectus abdominis, internal and external obliques, and transversus abdominis) and internal intercostal muscles for expiratory is always accessory.
The intrathoracic parts of the trachea and the bronchi narrow during expiration and widens during inspiration. Their cartilage support prevents them from total collapse. Still, flow rates may not be increased by forced expiration for most of the expiratory phase because the resulting increasing positive pressure in the thorax compresses the airway to a level that decreased airway size counters the increased force to expire [9, 10].

We searched the text of Vesalius’ Books I – *The Bones and Cartilages*, II - *The Ligaments and Muscles*, and VI – *The Heart and Associated Organs* of *De Fabrica* for references to these aspects of the respiratory physiology. For this inventory we used the digital copy of the first print of *De Fabrica* (1543) [3] and its English translation as provided by Richardson and Carman [11-13].

**Results**

*Vesalius’ instructions for in vivo demonstration of pulmonary movements*

Vesalius opened the very last chapter of *De Fabrica* entitled ’Some Remarks on Vivisection’, by stating that it is “appropriate that [medical] students should begin by dissecting the dead and then go on to inquire into the action and function of the parts by addressing a living animal” (quote on p. 263) (Figures 8.1 and 8.2) [13]. But beware, “for there is no point in trying vivisection unless one is a skilled dissector of the dead” (quote on p. 265) [13]. Among many other in vivo experiments [1], he described the visualization of the moving lung by two different approaches (Figures 8.3 and 8.4). For the first approach “in order to see the natural movement of the lung as it follows the thorax, cut away the cartilages of two or three middle ribs on one side, make incisions along the intervals between these ribs, and break off each rib by bending it outward. This makes an area through which you can inspect the lung on the undamaged side; for the membranes that partition the thorax in dogs are quite transparent and it is easy to examine through them the part of the lung that is still following the movement of the thorax and, after piercing carefully through the membranes, to see how this part of the lung as well ceases to move” (quote on p. 269) [13].

Alternatively, if he “decided to follow my more difficult procedure”, Vesalius made “in one side of the thorax [...] a longitudinal incision down to the rib bones roughly at the point where the bones turn into cartilage. Then I make transverse incisions along the rib bones, so creating an area over which I can denude the bones of the muscles that lie upon them; and then [...] I go to two of the intercostal intervals and remove the intercostal muscles in them from the tunic that undergirds the ribs, so that, using my hands alone, I can pull away half of the rib between these intervals from the tunic that undergirds the ribs, break it away from its cartilage, and bend it downwards to the side; this reveals the large cavity of the tunic that undergirds the ribs, which being transparent shows clearly the movement of the lung” (quote on p. 271-272) [13]. Only after some 120 more years, did John Mayow produce an artificial model of this in vivo experiment [1, 2, 7].
Figure 8.1: See opposite page for caption.
Vesalius’ records on respiration

On the physiology of respiration Vesalius opened with noting that “respiration is performed by two contrary movements, a movement of distension and dilatation that draws in, and one of constriction that evacuates” (quote on p. 283) [12]. He noted that “it is therefore obvious the lung follows the movement of the chest by the power of the vacuum when the chest is either compressed or dilated, it was necessary that muscles moving the thorax be constructed in order to expand or contract it” (quote on p. 283) [12]. Using the words “vacui potissimum ui sequitur” in the Latin original of this quote (on p. 287) [3] Vesalius showed to recognize that air is sucked in by the sub-atmospheric pressure that occurs in the lungs as the chest expands, approximately 100 years before Borelli did [1, 7].

By his vivisections he had shown the necessity of this vacuum between the lungs and thoracic wall by local resection of all layers of the thoracic wall while leaving the parietal pleura intact and subsequently inflicting a unilateral pneumothorax in the still breathing dog: “now I pierce through this tunic in its turn and point out that the lung on this side collapses even though the thorax continues to move as before. In order to reveal this more clearly I detach several more rib bones from their cartilages and open as much as possible of this side of the thorax so that the other part of the lung (which is still in the chest cavity and, being undamaged, is still moving nicely along with the thorax) may be seen through the membranes that partition the thorax; and I then pierce through these membranes in their turn and show that this causes an immediate collapse of the lung” (quote on p. 272) [13].

Likewise, he showed his understanding of the physiological mechanics of the pressure gradients during respiration when he recorded that “because of this [respiratory] function the rough artery [trachea] had to be made like a membranous channel, so it could
easily collapse when empty and distend again when full: for something that is to be filled solely by avoidance of the vacuum and then emptied solely by the force of compression has to be capable of distending and being compressed. There is general agreement that drawing breath of breathing in takes place by means of dilatation of the lung, and that this dilatation is simply the distension of its vessels-not of them all indiscriminately, but principally of the offshoots of the rough artery” (quote on p. 43-44) [13].

Figure 8.2: ‘In this figure the heart has been turned to the right [...]. H.H: Offshoots of the veinlike artery [pulmonary vein] running to the left part of the lung [...]. K: This part of the arterylike vein [pulmonary artery] travels to the left portion of the lung [...]. P: This portion of the great artery [aorta] bends downwards towards the spinal column [...]. R: This portion of the great artery travels to the throat [...]. Y: Stem of the rough artery [trachea]. [...]. i,k,l,m: Lobes of the lung. n,o: Transverse septum [diaphragm]’ (quotes on p. 11-2) [13].
Vesalius, furthermore, correctly distinguished between tidal ('natural') respiration and forced respiration by recording that “in the first place, there are two kinds of respiration, namely inhalation and exhalation, and each of these has two sub-types. One type of exhalation is natural and not forced; it takes place under the impetus of no more than a natural necessity. The other type of exhalation is forceful and vehement; it is known as blowing. Similarly one type of inhalation is natural, and the other is forceful and used for the voice and similar things” (quote on p. 295) [12]. Vesalius expressed his understanding of the active nature of tidal ('natural') inspiration and the passive nature of tidal expiration when stating: “the septum [diaphragm] by itself is the author of natural inhalation and exhalation, for the physicians have no doubt that when it contracts or tenses the chest is expanded and inhalation is produced; and again they affirm that when the septum is relaxed the thorax immediately collapses by its own weight and exhalation is the result” (quote on p. 295) [12]. This statement, furthermore, shows his correct appreciation of the diaphragm as the prime muscle of tidal respiration [9, 10]. Vesalius remark that “there is agreement also that breathing out takes place when the lung draws itself together, collapses upon itself, and becomes smaller, so thrusting out and expelling the air contained in its cavity (which means in the branches of the rough artery)” (quote on p. 44) [13], furthermore echoes our understanding of expiration as a passive phenomenon based on elastic recoil forces. 120 Years later, Mayow was probably still not aware of the importance of these elastic forces [2]. Vesalius continued that “from these facts anyone may readily deduce that the rough artery had to be constructed in such a way as to distend when we breathe in and to be compressed again when we breathe out” (quote on p. 44) [13], just like we now know the trachea to behave.

**Vesalius’ records on diaphragmatic function**

Following an extensive description of the anatomy of the diaphragm, Vesalius observed that “its function in moving the thorax is not obvious, nor am I aware of anyone who has left a proper account of it for posterity or undertaken deliberately to reproduce an earlier account ..[...]. The septum will not reveal its secrets to a casual examination; one must acquire a detailed knowledge of its position and form and must examine its function by means of vivisection” (quote on p. 293) [12]. He carefully explained how it causes inspiration “when it contracts ..[...] and draws the extremities of the false ribs toward its center, it constricts only the lower front portion of the thorax formed by the cartilages of the false ribs; but in doing so it dilates the rear part, which extends from the cartilage of these ribs to the vertebrae, and increases the intervals between the five lower ribs and also the sixth and seventh thoracic ribs (for the septum is implanted into their cartilages as well). This is how the transverse septum [diaphragm] dilates and distends the lower part of the thorax” (quote on p. 293-294) [12]. He subsequently presented one of the very few observations found in De Fabrica on in vivo human anatomy by adding “in order to follow more clearly what I am saying, first put your two hands on the cartilages of the false ribs, take a deep breath, and feel how the ends of the cartilages are pulled inward and upward. Then, leaving one hand in this position, spread out the other and place it at the back of the ribs, take another breath, and
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observe how the ribs are drawn apart in the vicinity of the spinal column and the cartilages move toward each other. If you have available a dog or some other animal, you should vivisect that and investigate the action of the septum; in such a procedure you must take care lest you think the animal is breathing out when it is actually breathing in, as you would be very liable to do if you paid attention only to the extremities of the false ribs and the places into which the septum is implanted” (quote on p. 294) [12].

Vesalius' records on forced respiration

Following his description of the 40 bilateral respiratory muscles he recognized in humans, Vesalius observed that “so greatly might the number of muscles of respiration be increased” (quote on p. 295)[12] for forced respiration. He recorded that “if the quality of the heart's heat increases, or if one needs more air for the voice or for some other purpose, straight away the first muscle [subclavian muscle], the second [anterior serratus muscle], the third and fifth in humans [superior and inferior posterior serratus muscle] ...[...]. will come into operation along with the septum” (quote on p. 295)[12]. These, in his view, constituted the accessory inspiratory muscles.

Likewise, he stated that “if there is need of more forceful exhalation, that is of blowing, for the voice, for shouting, or for playing flutes or trumpets or instruments of that sort, the outer intercostal muscles will gird themselves up for action along with the inner ones, for I assert that these too draw the ribs closer together and so constrict the chest. And they will immediately receive assistance from ...[...]. the one that stretches on either side to the side of the longest muscle moving the back [iliocostalis muscle], and also from the one that is hidden in the chest cavity beneath the cartilages of the true ribs [transverse thoracis muscle], and lastly the muscles of the abdomen themselves [rectus abdominis and pyramidalis, external and internal oblique, and transversus abdominis muscles], but not, surely, any of those that move the arm or the scapula” (quote on p. 295-5) [12]. Thus, it is clear which muscles Vesalius considered to be the accessory expiratory muscles. Regarding the role of the abdominal muscles as accessory expiratory muscles he explained that “if the obliquely descending muscles [external oblique abdominal muscles] are tensed, they slightly constrict the lower part of the thorax and so compress the thorax. The upright muscles [rectus abdominis and pyramidalis muscles] along with the obliquely ascending muscles [internal oblique abdominal muscles] draw the ribs downward and produce a considerable constriction of the thorax. The transverse muscles [transversus abdominis muscles] pull the ribs inward and hence operate to constrict the thorax” (quote on p. 295) [12].

Regarding the serratus muscles Vesalius remarked that “we (following other anatomists) shall describe [it] when we deal with the muscles moving the thorax” even though one may “conclude that it too moves the scapula” (quote on p. 244) [12]. Thus, he already realized that certain shoulder muscles may be viewed as accessory respiratory muscles as well as movers of the shoulder girdle when he wrote: “I would have you consider with some care whether the present muscle comes from the scapula and is inserted into the ribs and these vertebrae and so serves to move the thorax, or whether it takes origin from the ribs and these vertebrae and insert into the scapula and might therefore be regarded as producing movement
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of the scapula forward along the sides of the thorax” (quote on p. 285) [12].

Vesalius on the conscious nature of respiration

Vesalius stressed the difference between the autonomous nature of pulsation of the heart and the voluntary aspect of respiration when he observed that "the movement of the heart is a natural movement that goes on irrespective of our will; but respiration depends on our will, to the extent that we read of cases where people killed themselves by holding their breath. This is regarded as very advantageous for man, not merely in respect of the quality of life, but for life itself. For example, if respiration had to proceed with the same rhythm and consonance as the pulse of the heart, so that respiration did not depend on our own will and impulse, we would not be able to make speeches of long duration, and this would adversely affect our quality of life. Again, if we could not hold our breath while walking through smoke or dust or any bad and poisonous air, or through places contaminated by rotting corpses or sewers or other such causes, these things would very rapidly harm our life and damage our person. It follows as a consequence that the inhalation of air into our lungs through the rough artery and the exhalation of the heart’s fuliginous waste had to be subject to our will” (quote on p. 283) [12].

Figure 8.3: 'I turn now to the vivisection that I promised earlier to describe; for it you need a pregnant bitch or sow [...]. Lay the animal down on its back so that the front of its neck and the trunk of its body are facing upward with nothing obscuring them. Tie it down to the board as strongly as you can as shown in the illustration inserted at this point [...]. Amongst other things, you must take particular care that the upper jaw is tied firmly to the board [...]. making sure that the animal’s neck is stretched so as to be immovable and yet that the animal can breathe freely and make a noise. Before tying the animal down like this I usually, for an audience that is well versed in the dissection of the dead, go through the main things that they will see in this dissection so that I will not have to delay the procedure with a lot of lecturing or be constantly interrupting it’ (quote on p. 270-1) [13].
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Discussion

Vesalius’ misconceptions on the function of respiratory muscles

Vesalius’ *De Fabrica* primarily being a work on anatomy rather than physiology, his observations on the physiology of respiration stand out. He proved to have correctly grasped most of the principles of tidal and forced respiration. Furthermore, he recognized the internal and external intercostal, subclavian, serratus, iliocostalis, transverse thoracis muscles, and the muscles of the abdominal wall as respiratory muscles along with the diaphragm. Still, the remaining muscles that we currently recognize as (accessory) respiratory muscles [14] were correctly described anatomically by Vesalius, but he failed to note their respiratory function. Likewise, he failed to correctly interpret the mechanical action of some of the respiratory muscles he did recognize [12].

As such, Vesalius misunderstood the physiology of the diaphragm. He worded his misunderstanding in a rather sarcastic tone that, given our current knowledge, appears to backfire as misplaced arrogance when he wrote that he was “well aware that certain eminent men of our time, who have on occasion attended my dissections, contend that the proper movement of the septum is downward. They have failed to realize the implications of the fact that nerves from the spinal marrow in the neck insert into the upper area of the septum, of the very clear evidence afforded by vivisection, and also of the fact that when emptying our bowels we compress the thorax by avoiding inhalation, not expand it by continuing to breathe in; the latter would be necessary if the septum were drawn downward when the chest expands, so that it could then join the abdominal muscles in assisting excretion. The same thing is apparent when you breathe in very deeply but try to do so without allowing the cartilages or false ribs to move upward and inward, for when you forcibly hold them still in this way and take a couple of breaths, the area of the cartilages behave just as if it had been punched with fists. But I think that you also are familiar with these facts one way or another, and I have done so much arguing over these breathings in and out that sheer weariness impels me to lay down my pen” (quote on p. 294) [12].

Second, Vesalius was wrong in his inclusion of the external intercostals along with the expiratory muscles. He did so even though he recognized that “Galen opines in many places that the thorax is constricted and expanded by means of the intercostal muscles; and since there are two sets of these he writes that the outer muscles produce exhalation (which means that they draw the ribs together and compress the thorax), while to the inner muscles he ascribes the function of inhalation (which involves pulling the ribs farther apart and thus increasing the size of the chest cavity). But sometimes he was inconsistent, wanting the outer muscles to be in charge of inhalation and the inner ones of exhalation” (quote on page 290) [12]. “Being utterly devoted to Galen”, Vesalius continued, “I would not venture flatly to contradict his teachings, but even less would I express uncritical assent to them; it is a fact that thus far I have not been able to find out how the intercostal muscles, whether inner or outer, could possibly draw the ribs apart and separate them from each other. I have paid due attention to Galen’s vivisections and have tried them myself both alone and in public lectures
at Padua and Bologna, and they prove the exact reverse of what Galen teaches. In addition, the position, shape, fibers, and everything else to do with the fabric of the intercostal muscles, show quite clearly that these muscles draw the ribs together, not relax them” (quote on p. 290) [12]. It made him conclude that it is not “at all unreasonable that Nature should have created all the intercostal muscles for breathing out or constriction of the chest, since we need a stronger movement and impulse for blowing, speaking, coughing, sneezing, excreting feces, and assisting the expulsion of the fetus -in short, for compressing the chest- than for breathing in. That is why the muscles in charge of breathing in are few and weak” (quote on p. 290-291) [12].

In his mistaking the external intercostals for expiratory muscles, however, Vesalius stood not alone and the controversy regarding these muscles had not completely been resolved in all details, even in 1986 [2].

**Figure 8.4:** In this ‘picture of instruments for dissection’ Vesalius ‘depicted lying on top of a table a board that we find most useful in vivisection, and upon this board we have placed everything that one could possibly need for practical dissections and for anatomy in general [.]. B,B: Board suitable for performing vivisections. C,C: Various holes through which, depending on the size of the animal, we pass nooses to immobilize its legs and arms. D,D: The rings are for tying the animal’s hands and feet to. E: To this ring the upper jaw (but not the lower) is bound with a small chain to keep the head still; thus the voice and respiration are not impeded by the use of chains’ (quotes on p. 148-9) [12].
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Vesalius’ misconceptions on the functional anatomy of the trachea

Vesalius has likely been the first to report on positive pressure ventilation through a tracheotomy and on its life-saving function some 100 years before Robert Hooke repeated these experiments [1, 15, 16], when he instructed “in order to revive the animal, make a hole in the root of the rough artery [trachea], insert into it a reed pipe or hollow pen and blow into this until the lung rises and the animal starts, as it were, to breathe; it takes only a small amount of air in this living animal to inflate the lung to the size of the thoracic cavity. The heart then starts to beat again and nicely displays its various movements” (quote on p. 273) [13]. Still, he showed his misunderstanding of the exact physiological mechanics of respiration and the respiratory functional anatomy of the trachea when noting that “for these [respiratory] functions it would be sufficient that it [the trachea] be formed from a membranous and fleshy substance like the stomach, the gullet, or the arteries and veins, and it would not need the cartilages with which it is in fact so liberally endowed; and hence the conclusion is drawn that, so far as the attraction of air (cause by the vacuum), the consequent distension of its own body, and the expulsion of the air again by its own compression and narrowing are concerned, it is pointless for the Creator of the world to give it any cartilages at all. It is an insult to the genius of the Creator to imagine, as some do, that all the branches of the rough artery that distribute into the substance of the lung are made of cartilages that are complete circles in shape and that the structure of the rough artery differs here from where it lies alongside the gullet: these people have not realized that, if the structure of the rough artery were like that, the lung could not distend and relax properly, or rather that the branches of the rough artery could only become longer or shorter and could not increase their breadth” (quote on p. 44) [13]. On hindsight, Vesalius’ sarcastic arrogance backfired again as he continued that “hallucinations are also being suffered by those who assert that the rough artery was constructed to stand permanently open, not collapsed like the gullet, to facilitate the ingress and egress of air; these people not only ignore the opening and closing of the larynx but also are witless as not to have noticed that, if the rough artery and all its offshoots were permanently stretched open, the lung could never be compressed and dilated and nothing could be drawn into the rough artery by avoidance of the vacuum, since this requires that the artery have been previously collapsed. They should have learned this by considering bellows, where the design of the part through which the air passes is quite different from that of their cavity. The experts have made the cavity capable of distending and being compressed so that the bellows can be filled and emptied, but the nozzle is made rigid and hence cannot be compressed. If the bellows were rigid like this all over the whole point of it would obviously be lost, as the bellows would then be like a glass flagon. So much, then, for the membranous substance of the artery and the reason why it had to be membranous” (quote on p. 44) [13].

Conclusion

We conclude that Vesalius grasped most of the mechanical essentials of, and differences between, tidal and forced respiration even though he mistook some of the muscle’s mechanical fashion of action. In publicly recording his insights, more than 470 years ago, he laid a firm basis for the understanding of the physiology of respiration and the management of its disorders as we currently know them.
References