The Legacy of Adolf Eugene Fick for Exercise Physiology

Ramos Álvarez, Juan José[1]; Lorenzo Capellá, Irma[2]; Calderón Montero, Francisco Javier[3]

Abstract

Unintentionally, Fick's contribution to exercise physiology has been fundamental both to the understanding of important concepts and to the practical application. Adolf Eugene Fick proposed a method for the determination of the average cardiac output, based on the principle of conservation of the mass of an indicator. However, the way Fick's equation is expressed by the physiological of the exercise is misused because they establish as a dependent variable the oxygen consumption. Never would Fick have thought that his principle for determining cardiac output would be so fundamental for understanding and applying the body's response to exercise. Therefore, it really should be said: "by solving oxygen consumption in Fick´s equation you get a good conceptual approach to the physiological factors that determine this very important parameter in exercise physiology. This article aims to highlight Fick's true contribution to knowledge of exercise physiology. Indeed, by clearing out Fick's equation, simple mathematical models of cardiac output and the arterio-venous oxygen difference during exercise can be obtained. Finally, from Fick's equation it is possible to understand which are the physiological factors limiting the maximum oxygen consumption, one of the central parameters of exercise physiology.

Key words: Adolf Eugene Fick, Fick´s Principle, exercise physiology, cardiac output, arterio-venous oxygen difference, mathematical models

1. Introduction

As is often the case in medical history, the biography of **Adolf Eugene Fick** (1829-1901) is very interesting, although it is not appropriate here to describe the scientific background of this pioneer in physiology. For the interested reader, there is a vast amount of information about the scientific work of this eminent physiologist. However, this paper will focus on how his well-known principle for determining cardiac output has had considerable importance for the understanding of exercise physiology concepts.

Briefly, Fick had many facets that are difficult to find nowadays. He was a good mathematician and physicist, which allowed him to invent various devices for physiological measurements, such as the aneroid manometer, myotonograph and a galvanometer. This great training, so "disparate" at present, allowed him to reach a high level in physiology. Two of Fick's most outstanding contributions are: 1) the principles governing diffusion and 2) the determination of average cardiac output. Because of the impact it has had on exercise physiology, the determination of cardiac output will be explained in more detail.

Fick thought that diffusion was one of the most essential phenomena of living beings. However, it was not until the studies of the English chemist Thomas Graham that Fick was able to enunciate the well-known law of diffusion, which bears his name, although in fact, it should be called the Graham-Fick law of diffusion. Although Fick offered no experimental data, he had been studying the different factors that affect diffusion: surface, difference in partial pressures, thickness and diffusion constant).

Fick's second contribution is the subject of this article and is therefore developed in the following paragraphs. It is true that Fick's principle has been "misused". It is usual to express Fick's equation as follows, even in prestigious authors of exercise physiology(Levine, 2008):

---

[1] School of Sports Medicine, Madrid Complutense University, Madrid, Spain. E-MAIL: jjramosa@ucm.es
[2] Faculty of Education and Health, Camilo José Cela University, Madrid, Spain
[3] Faculty of Physical Activity and Sport Sciences, INEF, Madrid Polytechnic University, Madrid, Spain

$$\dot{V}O_2 = Q \times Difa - v\,O_2 \text{ (equation 1)}$$

This is a major conceptual error, as this mathematical expression of Fick's principle leads us to think that this physiologist devised the method to consider $\dot{V}O_2$ as a dependent variable. Anyone who has studied

Fick's principle knows perfectly well that $\dot{V}O_2$, together with the $Difa - vO_2$, are the dependent variables for

calculating average cardiac output. However, this form of expression of Fick's principle (equation 1) is certainly enormously interesting for understanding the body's response and adaptation to exercise and training, respectively.

We think that when the expression of Fick's principle is written as in equation 1, it should be said that *"by solving $\dot{V}O_2$ in Fick´s equation you get a good conceptual approach to the physiological factors that determine this very*

important parameter in exercise physiology". Although it is repetitive, we will proceed in this way throughout the article, in order influence interested readers in a true perspective of Fick's equation. Expressing the principle in the terms of equation 1 distorts Fick's "thinking". It never crossed his mind that $\dot{V}O_2$ was the dependent

variable. Beyond attending a gymnasium, before starting medical school, Fick's specific interest in exercise physiology is not known. Never would Fick have thought that his principle for determining cardiac output would be so fundamental for understanding and applying the body's response to exercise.

2. Principle of conservation of the mass of an indicator

An indicator is an organism's own molecule or a supplied substance that allows the calculation of the amount carried in the blood at a given point in the circulation. The mass of the indicator of a substance or molecule specific to the organism is the product of the flow of blood and the concentration at a given place in the circulation. Thus, the principle of conservation of the mass of an indicator states that if there is no gain or loss in a closed system, its mass at the entrance (afferent) is equal to its mass at the exit (efferent) plus the mass from the indicator (supplied or removed). A certain amount (M) of the substance may be added by the organ to, or extracted from, its afferent blood supply. Therefore, the amount of the substance leaving the system will be respectively higher or lower than the amount entering it:

$$F_a \; x \; [X_a] \pm M = F_e \; x \; [X_e] \text{ (equation 2)}$$

Where F is the flow, a and e afferent and efferent, respectively. The plus sign is used when a substance is added to, and minus sign when substance is extracted from, the afferent flow

3. Fick's Principle

Cleverly, Fick used the lung as the system and oxygen as the indicator. Since oxygen is added to the afferent (venous) blood, equation 2 is

$$F_v \; x \; [X_v] + M = F_a \; x \; [X_a] \text{ (equation 3)}$$

Where v and a are venous and arterial, respectively. Fv and Fa are equal because the amount of blood entering the lungs also leaves it, although strictly speaking, there is a normal amount of right-to-left shunt whereby some coronary venous blood flow and bronquial blood flow drains into the left ventricle, left atrium, or pulmonary veins. Hence, equation 3 is as follows:

$$F_a x [X_v] + M = F_a x [X_a] \text{ (equation 4)}$$

Rearranging and clearing

$$F_a = \frac{M}{[X_a] - [X_v]} \text{ (equation 5)}$$

Fa is the average cardiac output, so that equation 5 can be written as commonly known

$$Q = \frac{\dot{V}O_2}{[O_2]_{arterial} - [O_2]_{venosa}} = \frac{\dot{V}O_2}{Difa - v\,O_2} \text{ (equation 6)}$$

Where $\dot{V}O_2$ is the oxygen consumption in ml/min and Dif a-v O_2 is the difference in oxygen content between the arterial and mixed venous blood, expressed in ml/100 ml

For the calculation of $\dot{V}O_2$ the volume of the expired air, the oxygen concentration in the ambient and expired air are measured using a variety of equally valid methods. At present, it is relatively simple with automated air volume and composition analysis equipment. When the measurement of $\dot{V}O_2$ is technically difficult or impossible to be carried out, predicted values as estimated by various authors can be entered into the Fick equation in place of the measured value (LaFarge & Miettinen, 1970), taking into account the error that can be made(Kendrick, West, Papouchado, & Rozkovec, 1988). Any systemic artery may be utilised for the arterial blood sampling for determining the Dif a-v O_2, since the oxygen content of the arterial blood is uniform throughout the body. The mixed blood is preferably sampled from the pulmonary artery where the mixing is adequate. Sampling from chambers proximal to the pulmonary artery may introduce errors because of incomplete mixing.

The content of O_2 in the a(Collier, 1956; Defares, 1958) arterial blood is measured using various instruments such as the Van Slike manometer, Clark electrode and spectrophotometer. When the blood haemoglobin content is known, the oxygen bound to haemoglobin is easily obtained (1 gr = 1,36 ml at saturation). Knowing the haemoglobin saturation in the arterial and mixed venous samples, the arterial and venous PpO₂ (hence the amount of O_2 in physical solution) can be obtained from the oxy-haemoglobin dissociation curve. Nevertheless, failure to correct for the O_2 in physical solution causes a very small error in the calculation of cardiac output.

Obviously, all of the above constitute serious drawbacks for applying the Fick principle during exercise. For this reason, Collier and Defares(Collier, 1956; Defares, 1958)devised a method for determining cardiac output known as "CO_2rebreathing", based on Fick's principle applied to carbon dioxide (Collier, 1956; Defares, 1958). They thought of applying the Fick principle to carbon dioxide, that is, an indicator that is extracted from the organism. Apply equation 5 to the measurement of the amount of carbon dioxide:

$$Q = \frac{\dot{V}CO_2}{(CO_2)_{avenosa} - (CO_2)_{arterial}} = \frac{VCO_2}{Dif v-a\,CO_2} \ (equation\ 6)$$

Where $\dot{V}CO_2$ is carbon dioxide removed in ml/min and Dif v-a CO_2 is the difference in carbon dioxide content between the mixed and arterial blood, expressed in ml/100 ml

Briefly, this method is performed in a closed circuit (rebreathing) and the equilibrium between the partial pressures of CO_2 in the mixed venous blood and the alveolar gas is determined, once the compensation between the air contained in the circuit and the alveolar air of the subject has taken place. However, the method presents certain difficulties that are accentuated during maximum exercise (Auchincloss, Gilbert, Morales, & Peppi, 1991; Hackney, Sears, & Collier, 1958):

1) Determination of the concentration of venous CO_2. Various techniques make it possible to measure this parameter by assuming that alveolar PpCO₂ equals capillary blood PpCO₂ in the lung. However, despite the good correlation with other methods, any of the techniques (Defares and Collier methods)(Collier, 1956; Defares, 1958), in addition to being difficult to perform, present disadvantages.

2ª) Determination of the arterial CO_2 concentration. This parameter is estimated but not measured. The estimate is made from the CO_2 pressure values measured in the mouth, although some studies have shown that the estimate corresponds to the measured values(Auchincloss et al., 1991).

3ª) During peak exercise the source of errors can be considerable, because to calculate the CO_2 volume it is necessary to take into account the haemoglobin saturation and the pH of the mixed venous blood, parameters that during extreme exercise do not remain constant.

3.1 Fick's principle into physiological compression of maximum oxygen consumption

Solving Fick's equation (equation 6) provides an equation (equation 1) that explains some of the parameters that determine maximum oxygen consumption. As Calderón noted(Calderon, 2018), the $\dot{V}O_2$max is the result of the maximum integrated function of uptake (respiratory system), transport (blood), pumping and distribution (cardiovascular system) and utilisation (mainly muscles). In turn, cardiac output is the product of heart rate and systolic volume, and this is the difference between the final diastolic volume and the final systolic volume. Thus, equation 1 can be rewritten as follows:

$$\dot{V}O_2 = (EDV - (ESV) \times HR \times Dif\,a - vO_2 (equation\,7)$$

Where EDV is the end diastolic volume, also tele-diastolic volume (TDV), and ESV is the end systolic or tele-systolic volume (TSV)

However, Equation 7 is incomplete. In this equation, cardiac parameters (EDV, ESV and HR), partly circulation parameters (Dif a-v O) and blood parameters (Dif a-v O) are represented, but equation 7 has not considered respiratory parameters. For this reason, Calderón has proposed the following equation(Calderon, 2018):

$$(\dot{V}_I \cdot F_I O_2) - (\dot{V}_E \cdot F_E O_2) = Q \times Difa - vO_2 \,(equation\ 8)$$

Where $\dot{V}_I$ and $\dot{V}_E$ are the ventilation in inspiration and expiration; $F_I O_2$ and $F_E O_2$ are the oxygen fractions in the inspired and exhaled air. When considering $\dot{V}_I = \dot{V}_E$, equation 8 is simplified

$$\dot{V}_E \times (F_I O_2 - F_E O_2) = Q \times Difa - vO_2 \,(equation 9)$$

Matching the two equations $\dot{V}O_2 = \dot{V}_E \times (F_I O_2 - F_E O_2)$ and $VO_2 = Q \times Difa - vO_2$ is only intended to provide a more complete understanding of the physiological meaning of maximum oxygen consumption, as shown in Figure 2.

3.2 Simple mathematical models of the parameters of Fick's equation

Fick's equation not only allows us to understand the physiological significance of maximum oxygen consumption, but also to propose simple mathematical models of the response of cardiac output and arteriovenous oxygen difference.

3.3 Mathematical model for cardiac output

Identifying term by term, in equation 6, with those of a straight line, it must be that the slope (b = 1 / [arterial O2]) is the inverse of arterial oxygen concentration and the ordinate at the origin (a = Q · ([O2] venous / arterial [O2]) is closely related to the product of cardiac output by the concentration of oxygen at the pulmonary artery.
This simple model allows understanding that:

1) A greater slope implies a worse cardiac response and suggests a lower concentration of oxygen in arterial blood (1 / [arterial O 2]). Endurance athletes have a higher concentration of oxygen due to the adaptation process. Therefore, they have a lower slope. In well-trained subjects, the Q-VO$_2$ relationship is actually curvilinear, in agreement with reports by authors who used the dilution technique;
2) The oxygen concentration at the arterial level is constant;
3) The flow of oxygen (Q · [O 2] venous in ml / min) returning to the heart is kept constant.

3.4 Mathematical model of *Dif - v of O₂*

By substituting in equation 6 one gets an equation for Dif a-v O₂, that is a hyperbola

$$Difa - vO_2 = \frac{1}{a + \frac{b}{vO_2}} \,(equation 10)$$

Where the horizontal branch (a = 1/[O2] arterial) is asymptotic to the arterial oxygen concentration when the VO$_2$ tends to infinity. The fact that the relationship between dif a-v O$_2$/$\dot{V}O_2$ is a hyperbola is transcendental for the following reasons:

1) The maximum dif a-v O$_2$ is necessarily lower than the O$_2$ concentration at the arterial level;
2°) The concentration of oxygen at the venous level cannot fall to zero. The minimum value must correspond to the partial pressure of oxygen in the venous return blood of about 20 mm Hg, which would correspond to a saturation of around 20%;
3°) Taking into account the effects of temperature, CO$_2$ and [H$^+$] on the association-dissociation curve of haemoglobin, this minimum value of partial pressure of oxygen determines the "critical closure pressure" of the capillaries.

3.5 The physiological limits of Fick's equation for determining maximum oxygen consumption

Again, by solving Fick's equation, one can consider the parametric limits that may explain the $\dot{V}O_2$max. Several reviews and have been written about this issue(Bassett & Howley, 2000; Bergh, Ekblom, & Astrand, 2000; Saltin & Calbet, 2006; Saltin & Strange, 1992; Wagner, 1996) and it is not appropriate to analyse them here.

The controversy over whether the physiological limit focuses on uptake (respiratory system), pumping-distribution (cardiovascular system) or utilisation (muscles) is somewhat sterile. It seems coherent to think that an integrative physiological parameter, such as maximum oxygen consumption, is limited by all the factors that determine it.

Anyway, the analysis can be done in terms of equation 8 or 9. At maximum effort, the first member of the equation can limit the ability of tissues and organs to consume oxygen. In conditions of normoxia, the term $(\dot{V}_E \times (F_I O_2 - F_E O_2)$ may be sufficient to explain the lung limitation, while in hypoxia, it is necessary to consider the first term $(\dot{V}_I \cdot F_I O_2) - (\dot{V}_E \cdot F_E O_2)$ of equation 9. The ratio of $Q/\dot{V}O_2$ is not linear over the entire range of an effort, as noted in the section mathematical model for cardiac output. Under peak conditions, it can change the slope or even go down. To learn more about the factors that can change function $Q/\dot{V}O_2$ we need to look at equation 7, which shows the parameters that determine cardiac output. Both the filling (EDV) and the emptying (ESV) capacities can limit the ejection capacity. Similarly, and related to both EDV and ESV, heart rate can contribute to the change or decrease in slope of function. At high heart rates, filling and emptying times are significantly reduced. Finally, the asymptotic branch of the function (Dif a-v $O_2/\dot{V}O_2$ is a sufficient argument to condition the $\dot{V}O_2 max$.

In short, the legacy of **Adolf Eugene Fick** for people interested in exercise physiology (students, teachers and researchers) is unquestionable. Although of great application in understanding oxygen consumption, we believe that expressing Fick's equation in the usual terms is a conceptual error. If only to highlight **Adolf Eugene Fick** figure, we think it should be expressed in the following terms: "*by solving $\dot{V}O_2$ in Fick´s equation (equation 6) you get a good conceptual approach to the physiological factors (equations 7,8 and 9) that determine this very important parameter in exercise physiology*".

References

Auchincloss, J. H., Gilbert, R., Morales, R., & Peppi, D. (1991). The effect of progressive exercise on the equilibrium rebreathing cardiac output method. Med Sci Sports Exerc, 23(9), 1111-1115. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1943634

Bassett, D. R., Jr., & Howley, E. T. (2000). Limiting factors for maximum oxygen uptake and determinants of endurance performance. Med Sci Sports Exerc, 32(1), 70-84. doi:10.1097/00005768-200001000-00012

Bergh, U., Ekblom, B., & Astrand, P. O. (2000). Maximal oxygen uptake "classical" versus "contemporary" viewpoints. Med Sci Sports Exerc, 32(1), 85-88. doi:10.1097/00005768-200001000-00013

Calderon, F. J. (2018). Fisiología humana. Aplicación a la actividad física. Madrid: Ed Panamericana.

Collier, C. R. (1956). Determination of mixed venous CO2 tensions by rebreathing. J Appl Physiol, 9(1), 25-29. doi:10.1152/jappl.1956.9.1.25

Defares, J. G. (1958). Determination of PvCO2 from the exponential CO2 rise during rebreathing. J Appl Physiol, 13(2), 159-164. doi:10.1152/jappl.1958.13.2.159

Hackney, J. D., Sears, C. H., & Collier, C. R. (1958). Estimation of arterial CO2 tension by rebreathing technique. J Appl Physiol, 12(3), 425-430. doi:10.1152/jappl.1958.12.3.425

Kendrick, A. H., West, J., Papouchado, M., & Rozkovec, A. (1988). Direct Fick cardiac output: are assumed values of oxygen consumption acceptable? Eur Heart J, 9(3), 337-342. doi:10.1093/oxfordjournals.eurheartj.a062505

LaFarge, C. G., & Miettinen, O. S. (1970). The estimation of oxygen consumption. Cardiovasc Res, 4(1), 23-30. doi:10.1093/cvr/4.1.23

Levine, B. D. (2008). .VO2max: what do we know, and what do we still need to know? J Physiol, 586(1), 25-34. doi:10.1113/jphysiol.2007.147629

Saltin, B., & Calbet, J. A. (2006). Point: in health and in a normoxic environment, VO2 max is limited primarily by cardiac output and locomotor muscle blood flow. J Appl Physiol (1985), 100(2), 744-745. doi:10.1152/japplphysiol.01395.2005

Saltin, B., & Strange, S. (1992). Maximal oxygen uptake: "old" and "new" arguments for a cardiovascular limitation. Med Sci Sports Exerc, 24(1), 30-37. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1548993

Wagner, P. D. (1996). Determinants of maximal oxygen transport and utilization. Annu Rev Physiol, 58, 21-50. doi:10.1146/annurev.ph.58.030196.000321