



Joseph Milic-Emili and his contribution to respiratory physiology

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On Jan 8, 2022, Prof. Joseph Milic Emili (more simply called Milic) passed away at the age of 91. He was born in 1931 in the village of Sezana (Slovenia, at the border of Italy); he was destined to become a leading figure in the field of respiratory physiology and pathophysiology. He made his medical studies at University of Milano where he graduated in 1955 under the supervision of Professor Margaria (at the time the chairman of the Istituto di Fisiologia Umana) who introduced him to “*the quantitative analysis of the data making use of diagrams and mathematics*”; further, he became promptly aware to “*find himself among a unique breed of high level investigators*” (Milic-Emili 2002).

The histogram below (Fig. 1), shows the yearly scientific production of Milic over 58 years of work (Fig. 1).

It is noteworthy that, from 1956 to 1960 he published 48 papers (green columns); peak production being reached, in 1959; one shall therefore consider time spent in Milano as crucial for his scientific training and maturation. Many of these papers were published in Italian in an Italian journal, so they likely remained largely unknown (PubMed provides the complete list adding the English translation of the title). Milic’s interests covered a wide spectrum of the respiratory function: work of breathing, the first studies on esophageal pressure recording, the pattern of breathing in relation with respiratory mechanics; the range of conditions studied was very broad including rest, work, normal people, cardio-pulmonary patients, athletes and not athletes, without ignoring pregnancy. This formidable training ground allowed the jump to publish in international journals. He published in Journal of Applied Physiology the paper on the technique of esophageal pressure recording (Petit and Milic-Emili 1958), on the mechanical work of breathing (Margaria et al. 1960; Milic-Emili and Petit. 1960; Milic-Emili et al. 1962) and the

role of diaphragm studied by electromyography Petit et al. (1960).

In 1963 Milic joined Harvard in Boston and continued to work on refinement of the esophageal technique (Milic-Emili et al. 1964a, b).

In 1963 Milic was invited to join McGill by Dr. David V. Bates and spent there the remainder of his career; he chaired the Department of Physiology and became Director of the Meakins-Christie Laboratories from 1979 to 1994. At McGill, he got acquainted with the technique of radioactive gases and, thanks to his strong background in respiratory mechanics he felt “*for the first time in life that he was in full control of a research line*” (Milic-Emili 2002). In fact, this led rapidly to the development of the technique allowing to describe the gravity dependence of the regional inspired gas in the lung (Milic-Emili et al. 1966), of perfusion (Anthonisen and Milic-Emili 1966), of ventilation (Bryan et al. 1966) and of the ventilation/perfusion ratio Kaneko et al. (1966).

A further important paper was published aiming at estimating at which lung volume the airways tend to collapse being thus excluded from ventilation (the concept of “*closing volume*”). Measurement of “*closing volume*”, based on a single-breath of Argon, was presented as a simple and sensitive test for early detection of small airway disease (McCarthy et al. 1972).

In 1971 Milic published a seminal paper on pressure-flow generation by the respiratory system (Pengelly et al. 1971). The results indicated that the internal impedance of the respiratory system, while driven actively by the diaphragm, is high enough so that respiratory activity is relatively insensitive to external mechanical loading, i.e., it tends to maintain ventilation constant in the face of external mechanical loads (concept of “*intrinsic stability*” of the respiratory system). Phrenic activity was correlated with an easily measurable and reliable index of the central inspiratory drive, namely the pressure generated in the airways on sudden occlusion of the mouthpiece at 0.1 s after onset of inspiration (the famous P.1) (Whitelaw et al. 1975).

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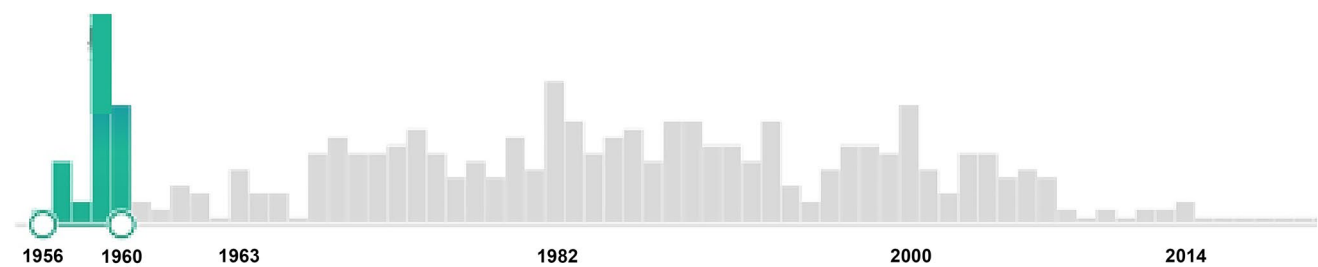


Fig. 1 Yearly scientific production of prof. Milic-Emili (redrawn from PubMed)

In 1972 Milic, recalling a paper of his early years (Milic-Emili and Cajani 1957), re-directed his interest to the relationship between ventilatory pattern and work of breathing. Milic proposed an ingenious way to relate the inspiratory drive with the timing components of ventilation (Milic-Emili and Grunstein 1976). Knowing tidal volume (V_T), the total duration of the respiratory cycle (T_{tot}) and the duration of inspiration (T_I), he re-touched the simple definition of ventilation (V_E) as: $V_E = \frac{V_T}{T_{tot}} = \frac{V_T}{T_I} \cdot \frac{T_I}{T_{tot}}$

In doing so, it became possible to correlate central power output (P.1) with inspiratory flow generation ($\frac{V_T}{T_I}$) and the timing of breathing $\frac{T_I}{T_{tot}}$ (that he defined as “duty cycle”).

Since 1990, Milic started considering respiratory mechanics in patients with acute respiratory failure due to severe chronic obstructive pulmonary disease (COPD). In 1995 a simple method was proposed to diagnose flow limitations based on the application of a negative pressure at the mouth during expiration: failure to increase expiratory flow rate was taken as an index of flow limitation (Koulouris et al. 1995). Anaesthesia was a largely exploited domain of research. An important paper (Zin et al. 1982) developed the methods to derive (experimental model in animals) compliance, flow resistance and thus the time constant of the respiratory system; the same methods was then exported to humans (Behrakis et al. 1985).

What people think of him

Milic has been regarded as an enlightened and innovative scientist. He devoted his life to research and this was done through a strategy based on three pillars: (1): scientific training, (2) developing the techniques/methods suited to his specific interest, (3) establish a priority in the sequence of the experimental approach. Milic accomplished this task behaving as undisputed leader capable of arousing enthusiasm in many young people. Over 58 years of work, Milic published 388 papers, with about 700 co-authors. A minor number of these co-authors did follow an academic way: by and large, most were young fellows involved in clinical work, coming to Montreal from all over the world to join a “high school

of respiratory physiology and pathophysiology” set up at McGill. As from the official note from McGill announcing his passing, Milic was many things: “*teacher, mentor, friend.... fierce competitor..... critic and antagonistic prosecutor, historian and philosopher.....He was an enormously talented and complex man.....he had that little twinkle in his eyes and he embraced life. He was one of a kind, and there will never be another like him*”.

What he thought of himself

Milic wrote two articles on his life entitled “*A life of passion and serendipity*” Milic-Emili (2002) and “*How It Really Happened, a Respiratory Physiologist by Hook or by Crook*” (Milic-Emili 2003). He mostly considered himself as a passionate “*methodologist*” and this was the kernel for his interest in developing new techniques to unravel unexplored respiratory physiology. As from his words on the occasion of his retirement he wrote: “*I found that, at this time in my life, the names and memories of my co-authors have become more important to me than the scientific content of my papers*”. This statement proves that he was able to establish relationships of sincere friendship and mutual esteem.

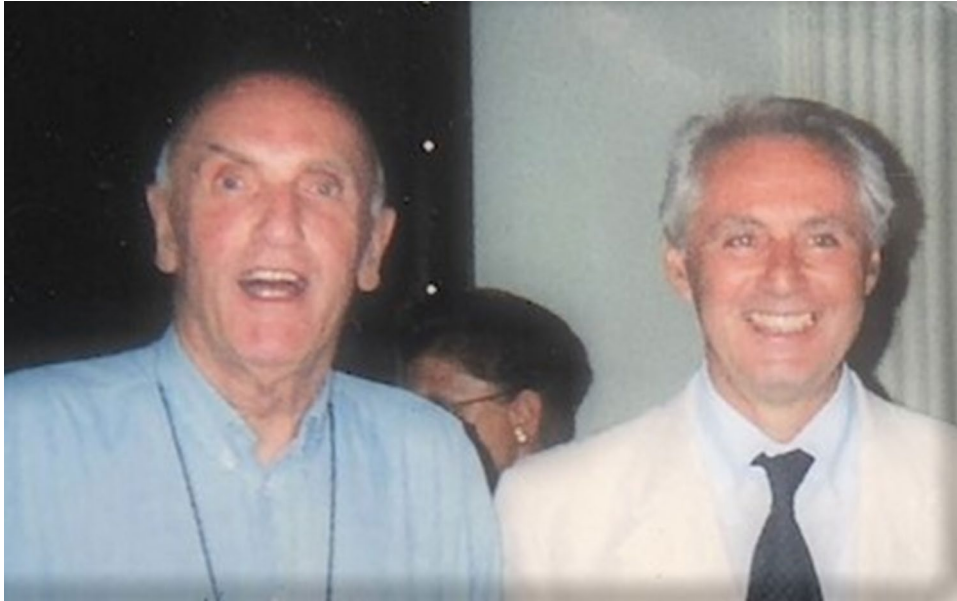
I wish to add a personal comment on what Milic wrote about himself: “*passion* is quite clear as he devoted his life to research. *Serendipity* is a rarely used word. According to the Webster’s dictionary, it indicates the “*apparent aptitude for making fortunate discoveries accidentally*”; on the same line was Julius Comroe (former Director of the Cardiovascular Research Institute, University of California School of Medicine in San Francisco) who maintained that “*serendipity is looking in a haystack for a needle and discovering a farmer’s daughter*”. Milic was a person who did not like to brag, he would never let his intellectual superiority be weighed. I like to think that he decided for a minimalist reading of his remarkable achievements by justifying his successes as many lucky occasions. Given the passion he put in his work, I’m prone to consider that *serendipity* was just the obvious consequence of his dedication to research that he kept indeed by “*hook and crook*” along all his life. This, I believe, is his

true legacy to young investigators, namely one's knowledge to become "*in full control of a research line*".

A note by the author

I joined McGill in 1973 and spent there almost 4 years; I shared with Milic, the eagerness to develop the equipment and the experimental procedure suitable to measure key

variables. At the time I was developing a new approach to model microfluidics at the level of the air-blood barrier and its dependence on lung mechanics. Milic always encouraged and provided useful insight. We became close friends, I hosted him in Italy on many occasions and spent a good time together. The picture below shows both of us attending Verdi's opera *Ernani* in Naples at San Carlo theatre in 2002. I will remember his optimism, his humour, his smile and his always deep gaze.



Author contributions GM wrote the whole paper.

Declarations

Conflict of interest I have no conflict of interest.

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