

Giovanni Nigro and the Naples's school: historical contribution to the knowledge of heart involvement in Duchenne/Becker muscular dystrophies

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It is now accepted worldwide that cardiac involvement in Duchenne and Becker muscular Dystrophies, is a constant feature. The concurrent impairment of the heart as a muscle in dystrophic process was an inspired idea by Prof. Giovanni Nigro ten years before the discovery of the dystrophin gene, occurred in 1987. This article is intended to be a recognition to him and to the Neapolitan School he directed for the contribution in the knowledge of cardiac involvement in the course of Duchenne (DMD) and Becker (BMD) Muscular Dystrophies and in DMD/BMD carriers.

Key words: dystrophinopathic cardiomyology, Duchenne muscular dystrophy, Becker muscular dystrophy, Duchenne/Becker carriers

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Giving honour to the memory of Professor Giovanni Nigro is not an easy task, considering the versatility of his character and his ability to be always 20 years ahead.

I had the chance to meet him at the 4th year of my medical degree at the Federico II Naples University, as he was my teacher in the two-year *Special Medical Pathology* course. I was immediately impressed and fascinated by his passionate lessons, especially those regarding the heart and muscular dystrophies. After passing the exam, I decided to carry out my thesis on muscular dystrophies. I asked him to attend his laboratory as an internal student and I was accepted.

I could never imagine how large could be the field that I was approaching, but from the first moment, muscle diseases – in the plurality of their aspects, myological, cardiological and genetic – came into my life as the most important subject.

Professor Nigro used to entrust internal students to his collaborators and to involve them in the research. I took part in the first census of muscular dystrophies he was carrying out in Campania. It was the second half of the 70s: I still remember the trips made from province to province in our region, consulting the lists of disabled people in the provincial offices,

and going house-to-house visiting patients to confirm or exclude the diagnosis of muscular dystrophy. The results were published in *Muscle & Nerve* in 1983¹.

Giovanni Nigro was basically a cardiologist, heart was his main interest, hence his studies on cardiac involvement in muscular dystrophies. At that time there were no available statistical programs, so I remember the long days we students spent together reporting on large cardboards the data of hundreds and hundreds ECG traces, which had to be manually processed for statistical purposes. This huge work let him hypothesize for first that in muscular dystrophies the heart is primarily affected as a “muscle”². However, his pioneering vision was accepted by the scientific community only after the discovery of the dystrophin gene³ and the demonstration that the protein is expressed in the heart, in the same quantity as in muscles⁴.

The cornerstone of his work remains the paper on the *Incidence and evolution of cardiomyopathy in Duchenne Muscular Dystrophy*, published in the *International Journal of Cardiology* in 1990⁵ and worldwide cited. In that paper, thanks to the three-four decades of experience with patients affected by Duchenne/Becker muscular dystrophy,

he showed that cardiomyopathy associated with muscular dystrophies is constantly progressive and evolves passing from a pre-symptomatic condition (P type)⁵ to dilated cardiomyopathy and intractable heart failure⁶ (Fig. 1).

The discovery of dystrophin strengthened his hypothesis that dystrophinopathic cardiomyopathy (DCM) can present with different clinical pictures based on the dystrophin alterations. He speculated that DCM is caused by a complete absence of dystrophin at the myocardium as in skeletal muscles in Duchenne patients, while in Becker (BMD) patients it is caused by a reduced/abnormal amount of dystrophin⁷. He pointed out in the latter how cardiomyopathy is frequently observed even before the age of 30 years; dilation can be the first manifestation of heart involvement and underlying myopathy⁷; the onset of arrhythmias can cause sudden cardiac death⁸⁻¹⁰; life expectancy is severely conditioned by the presence of cardiomyopathy^{8,9} and finally how the onset and severity of cardiomyopathy is closely related to the type of dystrophin gene mutation¹¹.

The presence of a puzzling dilated cardiomyopathy in the mother of a Duchenne patient he followed for many

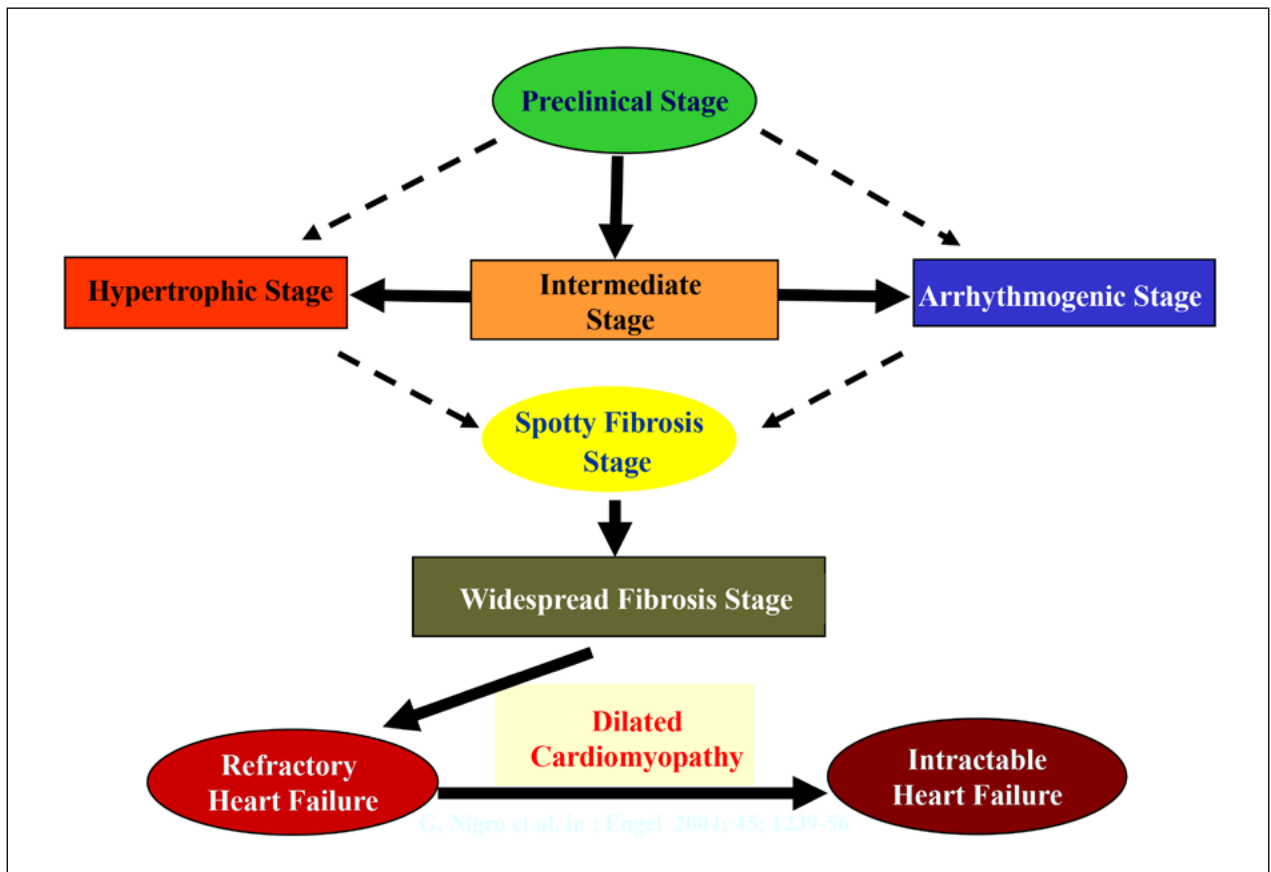


Figure 1. Evolution of Dystrophinopathic Cardiomyopathy according to Giovanni Nigro (1977).

years, led him to analyze the ECG traces and the echocardiograms of about 200 women obliged carriers of DMD/BMD, showing that cardiomyopathy is a common feature in this group of individuals and often the only marker of their carrier status^{12,13}.

Therapy was very important to him. He didn't used to passively follow the new "emerging" guidelines, but he strongly believed in the importance of a personalized therapy according to the patient clinical condition. For this reason, in the last 5 years of his career, after 45 years of teaching *Special Medical Pathology*, he asked and obtained to teach *Medical Therapy* to the 6th year students in the same University.

He used to teach that in all pathologies, but especially in muscular dystrophies, it is necessary to have a holistic view of the patient, hence the need for a multidisciplinary approach with the participation of experts from various disciplines, myologists, cardiologists, pneumologists, orthopedists etc. This model was immediately implemented by his staff, and "rediscovered" after 30 years as the ideal approach for muscular dystrophies¹⁴.

Professor Nigro used to involve patients on the results of his own and others' research as well as any pharmacological new treatment¹⁵⁻¹⁷, once excluded the possible

side effects. He was open minded to any therapeutic possibilities, from the minimal orthopedic surgery suggested by Rideau in France in the early 80s¹⁸⁻²⁰ to the steroid therapy proposed at the Munich Congress in 1990, to the aminoglycosides perspectives.

The collaboration between Poitiers and Naples has always been intense and over time more than 200 DMD children underwent the same surgery also in Naples, getting an average extension of walking about 3 years, at a time when there were no other therapeutic options.

He immediately believed in the power of steroids to improve muscle strength in Duchenne boys, and indeed he was convinced that minimal surgery and steroids would act synergistically to improve the outcome. Likewise he was the first to believe and to practice the prophylactic use of ACE inhibitors, to delay the onset of overt cardiomyopathy in Duchenne and Becker patients¹⁵⁻¹⁷ as far as the first in Europe to treat with gentamicin four patients with DMD caused by a stop codon dystrophin gene mutation, with promising results²¹.

After about 20 years, during which more than 250 Duchenne patients had been treated with steroids (deflazacort²² rather than prednisone), ACE-inhibitors and anti-oxidants, he was able to affirm that this treatment,



Figure 2. Prof Giovanni Nigro together with his collaborators and some of his internal students.

associated with physical rehabilitation, was effective not only for the motor function, but also on the onset and severity of cardiomyopathy and on the decline of the vital capacity curves^{15-17,23}.

All his thought is included in the chapter on cardiomyopathies associated with muscular dystrophies, in the textbook “Myology” published by Andrew Engel in 2004²³, in which he was happy and honored to collaborate.

It was a privilege and an honour for me to have met and worked for so many years with such a *special* person. He has always put the patients and their families at the center of his interests, and it’s thanks to him that I had the chance to meet so many special people.

I’d like to conclude this brief and certainly lacking tribute to Professor Nigro, with one of his sentences which summarizes his close relationship with muscle diseases: “Myology? The passion of a lifetime!”.

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