

Why Pathologists Have Not Discovered ARVD?

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Pr Robert Myerburg of the University of Miami Hospital in the United States notified me via fax on March 11, 1996 about a 17-year-old girl from a prominent family of Florida who died suddenly without warning or previous symptoms. The issue was to determine the cause of this sudden death since another young individual of this family had died without obvious cause.

Doris Toran-Goldman, President of an American association called "Care," centered on the sudden death of youngsters as a consequence of the "Long QT syndrome", learned of this catastrophe from the media. She, herself, lost two children aged 24 and 27 from this condition. Doris informed the girl's family about the possibility of this diagnosis, and indicated that Dr. Myerburg was the most qualified expert in this field. The fax also announced the arrival of a histological glass slide of the left ventricle by "Federal Express". The presence of debatable anomalies here raised concerns whether or not this histological structure could be sufficient to explain sudden death.

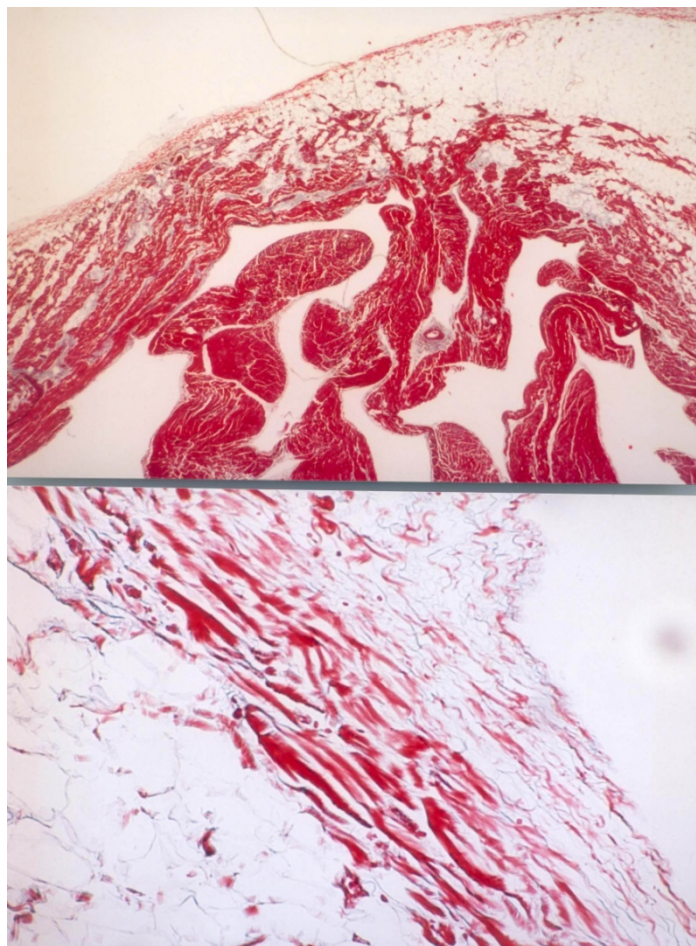
The slides containing the histological preparation arrived shortly thereafter, as envisioned, a few days before my planned departure for Orlando. I was to attend the scheduled annual meeting of the American College of Cardiology of 1996.

Time constraints did not allow me to meet with my pathologist, Dr. Fabrice Fontaliran. However, on the slide of this structure, it was obvious that fibrosis and fat were present in some areas of the left ventricle. Therefore, the existence of an "anomaly" was unmistakable. My immediate response was to ask, "can you send a complete standard 12 lead electrocardiogram as well as the histological samples of the right ventricle?" Dr. Myerburg answered by return mail that there was no electrocardiogram available because the girl never presented any abnormal symptom before the misfortune. I was told that I could inspect the right ventricle if I would be able to meet him in Miami after the Orlando meeting. As Dr. Morales of Jackson Memorial hospital was Chief of the University section of Pathology and Forensic Medicine he was in position to obtain the RV samples from the Medical Examiner of Broward County.

On arrival in Jackson Memorial Hospital, Dr. Meyerburg explained to me that this tragic account had been reported in the press. He showed me the ECG's of close family members, some of whom had QT interval higher than the normal limits of extreme cases without being able to be clearly classified them as "Long QT Syndrome". Next we visited Dr. Morales, Chief of the Pathology service, who obtained the histological slides from the Medical Examiner of Broward County where the victim lived.

The examination of right ventricular cuts was already strongly evocative of dysplasia upon direct view. When the histological cuts were examined under the microscope, it was obvious that there was an important fat dissociation present in the external layers of the right ventricle. Fibro-fatty tissue with

residual strands of myocytes was also present, further affirming the diagnosis of Arrhythmogenic Right Ventricular Dysplasia, which could explain sudden death.



Note the thin rim of surviving fibres in the subepicardial layers

During this same day, we also visited Dr. Joseph H. Davies, Chief of the Department of forensic medicine in Miami. The laboratories were located in a structure akin to concrete – a gray-pink colored blockhouse surrounded by carefully placed palm trees. The first and last names of Dr Davis were impressively encrusted in black iron letters, 10cm high, in the same grey-pink concrete construction beside the institute door. Perhaps this gave an impression of power, the image of America which I had never seen anywhere else. This left me even more curious to meet Dr Joseph H. Davies. This man, on the verge of

retirement, met us at the entrance of his institute. He appeared to me, as did the image of his workplace, powerful and imposing, dressed in a lab coat so white it glistened in the bright Miami sun. On the small pocket of his impeccably ironed, immaculate lab coat, one could see his name embroidered in red by a sewing machine, the finest quality being evident. It was a sewing technique that gave the illusion of binding words together - a handwritten style of mechanical writing. This is a very particular and characteristic style of American technology. Each time I see this, I feel extremely satisfied. This seems to me the marker of a real academic medical standard in the USA!

Dr. Myerburg had praised Dr. Davies' competence and long established expertise. I estimated him to be the very great expert on the determination of any kind of death conferred by his function. He had two cases in his collection, father and son who died suddenly. The son had had a retrospectively evoked clinical diagnosis of dysplasia. The perfect staining of hematoxylin eosin and trichrome made it possible, in these two cases, to find what corresponded for me to the indubitable marks of right ventricular dysplasia. There were other cases which perplexed Dr. Davies. We proceeded to thoroughly discuss his slides, specifically the significance of fat in the heart, and particularly in the right ventricle. We also discussed dysplasia compared to physiological fatty tissue, and finally, the significance of the inflammatory phenomena.

Within a very short time, we found ourselves involved in a discussion, which reminded me of a previous one a few years earlier with the famous Italian pathologist, Pr Lino Rossi of Milan. He invited me to his sumptuous Milanese residence and showed me a brawn, wooden cabinet located in the middle of his dining room. Inside this piece of furniture were drawers, easily accessible, containing skillfully arranged Kodak slides collected during his long career. Some boxes of slides were tagged "unclassifiable". All showed a large quantity of fat on the right ventricular wall. These had been obtained from rather young subjects or rather old subjects, who died suddenly, as well as from other non-cardiac cases.

The same story came also from Maurice Lev of Chicago, himself being one of the most renowned American pathologists. I absolutely wanted to know his opinion; therefore, I made (in 1986) a special detour during one of my trips in the US to visit him after he had relocated for a while to Brown-Mills, New Jersey. I invited him for dinner in a fine restaurant along with his life long assistant, Dr. Saroja Bharati.

Before the food even arrived at the table, I started to speak, asking a direct question on the significance of fat in the heart. To my strong surprise he evaded the question and spoke of something else. Saroja was saying nothing, but was just looking at him, listening very politely and respectfully to everything he had to say regarding general matters. I was quite disappointed to have made a special trip to visit the “old pope” of American pathology, and to have invited him in one of best restaurants with my own money, only to receive no answer to this critical question. Abruptly at the end of the meal, Maurice Lev exploded with a strong and unexpected voice. “Dr Fontaine”, he said, “we cannot answer your question because fat in the heart is a totally unclear phenomenon which does not fall into our area of expertise. I am interested in the conduction system of the heart and my assistant Saroja has some expertise in congenital heart defects, but fat in the heart is not something we understand. You are young, so it is your time and your responsibility to work on this. If you solve this problem - the significance of fat in the heart - you will solve one of the most intriguing problems of heart pathology”.

It seems necessary for me to introduce an epistemological reflection of interest here. I have often wondered why these two excellent pathologists (and others such as Jessie Edwards, who also had unclassifiable slides, and William Roberts, who was the closest to isolate ARVD), with such an immense knowledge of the histological structure of the heart, and a perception of “something special”, could not have identified the disease.

At the present time I have the answer to this question: On the one hand, the human myocardium, even that considered “normal”, is dissociated de facto by fat in a large proportion of

individuals, on the other hand, a very low number of subjects having this anatomical anomaly are likely to express severe rhythm disorders. In addition the presence of fibrosis (interstitial fibrosis and not replacement fibrosis) is necessary for a positive diagnosis of ARVD. In some patients this fibrosis is minor and only found after the screening of multiple glass slides.

Eventually, ARVD was identified through a completely different approach. It was finally my electrophysiological concerns when I sought to understand the electrogenesis of late potentials, along with the understanding of the mechanisms of reentrant ventricular tachycardia, which forced me to propose a new term to isolate the disease. Therefore the need for a new entity was the result of establishing a relationship between several different things - the operative view of the beating heart covered by fat with clearly visible myocardial atrophy after surgical ventriculotomy, ventricular tachycardia surprisingly originating in the right ventricle as ascertained by epicardial mapping, the young age of mostly male patients, and a normal left ventricular function. All of these concepts put together seemed to me specific enough to introduce the carefully chosen term of Arrhythmogenic Right Ventricular Dysplasia (Stanley Robbins)

A few hours remained before my departure for the airport and return to France. I was intrigued by the history of the prominent family from Florida. I thought the victim to be a young woman associated with a reputed company businessman, or a well-known political tycoon. By chance, I passed the public library of Miami, entered, and inquired about the case of a girl who died suddenly at the age of 17 years. This could most likely be found in the local newspapers. I was assured that such a search was possible, but it would require a 48-hour wait! However, someone showed me how to enter key words on the local computer to help with my search. I entered the following: teenage girl, sudden death, Florida. In seconds, I had obtained 5 articles published in the “Miami Herald” pertaining to the sudden death of a girl at the age of 17 years, name of Krissy Taylor, whose career had been as a “top model”. She was the younger sister of another model extremely well known in the

USA named Niki Taylor. While investigating on the Internet, it was possible to also obtain a series of images of Niki and Krissy Taylor. I immediately stored one convincing image of Krissy on a diskette to save for regeneration in Paris as a precaution. Krissy Taylor had, in particular, made the first page of "Ocean Drive" a well-known women's magazine.

During my visit in Miami, I asked for additional glass slides of both the right and the left ventricle for my personal collection. This was for the purpose of my re-examination of these documents with my complete attention in order to confirm the diagnosis after returning to my homeland. Some time later I learned that the correct diagnosis of ventricular dysplasia did not satisfy the Medical Examiner of Broward County. He preferred the diagnosis of asthma, because he had observed suspect zones of the pulmonary parenchyma during a very attentive examination by electron microscopy. However, Krissy's pediatrician had never formulated this diagnosis. Although she admittedly used nasal spray from time to time when she experienced breathing difficulties, a diagnosis of asthma had never been suspected.

A rather sharp discussion began between the family, brought on by the difference in opinions between Dr. Myerburg and the Medical Examiner. The M.E. did not want to abandon his diagnosis of asthma. This is what led Dr. Myerburg to send the histological cuts to Walter Reed Hospital, Department of Pathology in Washington, DC. This is the famous Armed Forces Institute of Pathology located at Bethesda near the Federal Capital. There, the diagnosis of dysplasia had been discussed, implying that the anomalies observed could be due to the dysplasia of the right ventricle, but could also be a normal variant (cf supra).

These two opinions were revealed to me within time. I then decided, knowing the American way of thinking, that the implementation of my diagnosis might remain unrecognized. I wrote a letter (privately requesting Dr. Myerburg not reveal my identity) to suggest sending the histological material to three teams which I knew throughout the world: Pr Morie Sekiguchi

in Matsumoto City, Pr Robert Anderson of the Imperial College of London, and finally Pr Gaetano Thiene of the University of Padoua. This was accompanied by the reminder that the dysplasia was a familial disease. If this diagnosis was finally confirmed after the death of another suddenly deceased family member, he could be prosecuted for "failure to make the diagnosis of ARVD in a family member". The effect of this letter made the point. Everyone without need to send the histological documents to the international experts accepted the diagnosis of dysplasia.

Meanwhile, the history of Krissy Taylor was diffused on the Internet implying that her death had not been as mysterious as originally thought. Circulating rumors, due to incorrect information, of a drug overdose or liquid protein diet were false.

Subsequently, nearly two years after Krissy's death on July 2, 1995, the family decided to reaffirm the information by publishing an article in "Ladies Home Journal". Her mother explained the circumstances of Krissy's death in this magazine, as well as the contribution of a French expert regarding the diagnosis. The family also decided to draw the attention of other parents to focus on the importance of making ECG's a systematic practice for their children's health care. Indeed, it is known in dysplasia, in the long QT syndrome, in hypertrophic cardiomyopathy and in other genetic cardiac conditions of the young person, that there are anomalies of the electrocardiogram which should draw special attention. If the diagnosis had been evoked, perhaps it would have been possible to avoid the premature fatality of Krissy, provided that these electrocardiograms were interpreted by a cardiologist knowledgeable of the signs of this disease.

Occasionally, precise measurements are required of the duration of QRS complexes in the frust form of the disease. The construction of specific algorithms is theoretically possible, but should only be considered in a correctly structured research program (now on its way as recently requested in Circulation 5/12!)

This event encouraged me to search further for ECG anomalies among close family members for identification of the

“obligatory carriers” of the precise genes of right ventricular cardiomyopathies. Some of them presented small ECG

anomalies (Epsilon waves) which would have gone undetected by any contemporary academic cardiologist.