AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

This issue of AMPS QT is dedicated to the memory of Dr. Arthur J Moss who passed away last February at the age of 86.

It was my privilege to meet Arthur back in 1989, when I moved to Rochester with my wife Alessandra right after my graduation at the Polytechnic of Milan, and where I stayed until 1994 to complete my doctoral studies at the University of Rochester. Arthur was an exceptional person, who respected everybody regardless of social and cultural background, and who was always welcoming new fellows joining his Herat Research team with a special warm. He undoubtedly shaped me as a person and was a key mentor for my professional career.

We welcome Dr. Wojciech Zareba as the author of the leading article for this special issue. Dr. Zareba moved to Rochester in 1991 and is the current Director of Heart Research Follow Up Program. Having worked with Arthur for more the 25 years, he is truly the best and most entitled scientist to provide a thorough profile of Moss's professional career. I shared three great years of work with Wojciech, with his wife Grazyna and their daughter Caroline, and I want to personally thank him for his contribution on this issue.

Arthur had great vision. As a young biomedical engineer, I had the unique opportunity to join a group where the collaboration between the "engineer" and the "clinician" was an accepted routine and a natural way of work, at a time where this type of interaction was not yet a common or an obvious practice. In this regard, it is a special honor to host a contribution from Mario Merri, the very first engineer that joined the Moss lab. After his Rochester years, Mario pursed an exceptional career at the European Space Agency in Germany, and even after 30 years, the publications and brilliant ideas from Mario and Arthur are still widely referenced and used as landmarks for repolarization computerized analysis. After Mario, and after myself, other engineers followed and continued the tradition. I want to mention another two Italians, Laura Burattini and Martino Vaglio, but most of all Jean-Philippe Couderc, who since 1996 is strongly in command of the engineering operations.

Last, but not least, I must thank another special friend and research colleague tightly linked to the memory of Arthur: Dr. Emanuela Locati from Milan. Since the early 80s, Emanuela has been a very close friend of Arthur and surely was one of the key persons who helped trigger all the scientific collaborations that developed in these last 30 years.

Arthur's loss did not go unnoticed and in the last few months many meaningful remembrances have been written. This newsletter wants to be a further tribute to a great man and inspirational mind. Even AMPS would not be what it is today without the Arthur's guidance and always enthusiastic advice.

Fabio Badilini, Chief Scientist, AMPS LLC

A Noteworthy Contribution:

By Wojciech Zareba, MD, PhD, Professor of Medicine/Cardiology, Heart Research Follow-up Program, Rochester, NY, USA.

On February 14, 2018, we lost Dr. Arthur J. Moss at the age of 86 years, great researcher and leader in the field of cardiac arrhythmias. Dr. Moss was born on June 21, 1931. He graduated with psychology degree from the Yale University in 1953, and Harvard Medical School in 1957, and after his military service he started working at the University of Rochester Medical School in 1961 till the last days of his life.

Dr. Moss devoted his life-long clinical and research career to fighting heart disease, helping patients and conducting research to advance the field. Already in 1962, at the beginning of his cardiology training, Dr. Moss published a paper in the New England Journal of Medicine (NEJM) on the closed-chest cardiac massage in the treatment of ventricular fibrillation in 3 acute myocardial infarction patients successful resuscitated (Moss et al 1962). His devotion to fight sudden cardiac death persisted for the next 50 years.

Dr. Moss conducted numerous studied to improve the risk stratification of patients after myocardial infarction. In 1970-ties he received an NIH grant to conduct a study called The Multicenter Postinfarction Program (MPIP). This multicenter study enrolled over 800 patients and contributed to very important findings that later established the field of primary prevention of sudden cardiac death. MPIP showed that the importance of low ejection fraction in predicting mortality (Moss et al. 1987). In collaboration with Dr. Tom Bigger, the MPIUP project demonstrating the prognostic significance of frequent ventricular premature beats and nonsustained ventricular tachycardia (Bigger 1986). In 1987, Holter data from the MPIP study served to demonstrate the prognostic significance of heart rate variability (Kleiger 1987), the field that blossomed for the next 30 years. These advances contributed to common clinical use of Holter monitoring to document ventricular arrhythmias for risk assessment purposes.

In 1970-iest Dr. Moss was attracted to the concept of implantable cardioverter-defibrillator (ICD) developed by Dr. Michel Mirowski and his team. He became scientific advisor of Dr. Mirowski and subsequently he designed one of the first clinical trials with an ICD: the Multicenter Automatic Defibrillator Implantation Trial (MADIT). This trial was utilizing risk factors for sudden death established in the MPIP study: low ejection fraction and nonsustained ventricular tachycardia which together with inducibility of ventricular tachycardia identified a very high risk group of patients. The trial demonstrated that ICD treated patients had reduced mortality by over 50% in comparison to conventionally treated patients (Moss et al. 1996). The MADIT II trial (Moss et al. 2002), which followed, showed a 30% reduction of mortality in patients after myocardial infarction with just low ejection fraction ≤30% as unique risk stratifier. This study contributed to a frequent clinical use of ICDs for primary prevention of mortality. Following successful COMPANION trial conducted by Dr. Bristow and colleagues (Bristow et al. 2004), Dr. Moss conducted the MADIT-CRT trial, which tested ICD with cardiac resynchronization therapy in mild to moderate heart failure patients with NYHA class I and II patients with ejection fraction ≤30% (Moss et al. 2009). A 30% reduction in the primary endpoint of heart failure events or death was observed with even more pronounced benefit in patients with left bundle branch block (Zareba et al 2011). The MADIT II trial showed that ICD patients frequently experience inappropriate therapies (Daubert et al. 2008). The MADIT RIT (Reducing Inappropriate Therapy) followed with evidence for beneficial role of innovative ICD programming at higher rate and delayed device therapy (Moss et al. 2012).

In 1971 (Moss et al. 1971), Dr. Moss described new method of treatment of long QT syndrome (LQTS) patients: left cervivco-thoracic ganglionectomy (surgical procedure to diminish risk of cardiac arrhythmias). At that stage there was no treatment for the LQTS, beta-blockers were not yet used. In 1979 together with Dr. Peter Schwartz he established the International LQTS Registry to study this rare disease (Moss et al 1991). This registry resulted in very significant advancements in the field of the LQTS and cardiac arrhythmias (Moss et al. 2003).

Dr. Moss appreciated the role of electrocardiogram (ECG) in daily practice and in research. His long-standing interest in the LQTS led to numerous papers focused on the importance of QT interval in diagnosis and prognosis of these patients and subsequently influenced the field of drug-induced QT prolongation. The 1992 study by Merri and Badilini focused on detailed assessment of repolarization in electrocardiogram and its components became the landmark benchmark for hundreds of subsequent studies focused on QT and ECG parameters in drug safety (Merri et al. 1992). In 2008 study by Martino Vaglio, LQTS electrocardiology was further enriched by the study on quantitative assessment of T-wave morphology in LQTS by genotype (Vaglio et al. 2008) and by Jean-Philippe Couderc documenting the importance of T wave morphology in drug-induced QT prolongation (Couderc et al. 2008). Mario Merri, Fabio Badilini, Laura Burattini, Jean-Philippe Couderc, and Martino Vaglio are engineers who benefited from a great vision by Dr. Moss to bring clinicians and engineers together to the table with the main goal to advance the field of electrocardiology as they successfully did.

Dr. Moss was excellent clinician with a very successful academic career full of teaching and successful research. His visionary approach to research, leadership, best seen through the studied and trials mentioned above, was unique. He always enjoyed good discussions and led them in the right directions to advance the though process. He will be missed.

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Rochester's Heart Research Follow-up Program back in 1994. Dr. Moss in on the right, while Dr. Zareba is at the center. In the foreground are Fabio and his wife Alessandra.

A smiling Dr. Moss, talking at the phone in Hellen Wood Hall, 1993.

Other Contributions

Mario Merri, PhD, ESA/ESOC Darmstadt, Germany

We could write pages and pages on his incredible scientific intuitions and the many research achievements, but the truth is that in our hearts we have great admiration of Arthur as a person. A very positively complete person: a friendly leader, a thrusted advisor, a wise guide, in other words an example to follow. We have always appreciated his openness and anti-snob attitude with which he welcomed us, 2 unknown young students from Italy, in his world-renowned lab in Rochester. We distinctly recall the first contact that we had with Arthur: I (Mario) just called him in my broken English in October 1986 about 2 months into my Ph.D. at the University of Rochester (Michela was still in Italy at that time). I introduced myself and the projects we had contributed to back in Italy. At the end of the call, he simply invited me to visit him to better explain our ideas. In the meeting that followed, he immediately had the intuition that his experience and our technology could well marry together and invited us to join his lab. Successively, he gladly accepted to be the relator for our theses. This would had been unthinkable in Italy in those years (and probably even today) as no famous cardiologist would have never spoken to a simple student. Even more, he did guide us as a father during our three years in Rochester. He was just great!

Now that we have progressed in our careers, Arthur's teachings are part of us and we try always to give back what we had received with younger people who we professionally encounter. It makes a big difference and gives us a lot of satisfaction when some of these people develop a sincere respect for us that is not linked to the hierarchical relation, but rather on thrust and genuine respect.

Grazie Arthur! Michela and Mario

Vienna, 1988. Mario Merri and Dr. Arthur Moss.

Emanuela T. Locati, MD, PhD, Research Consultant, Grande Ospedale Metropolitano Niguarda, Milano, Italy.

My knowledge with Arthur Moss dates as far back as the Summer 1983, when I first attended Heart Research Laboratory in Rochester, just after my graduation from Medical School in Milan, and I feel this visit represents a true cornerstone in my life. Since then, I was continuously in contact with Arthur, who I feel not only as a teacher, but also as master and a guide, almost as a foster father. With Arthur at Heart Research, I built my first experience as a researcher and a physician, and in the years, I had always found there an atmosphere of exciting, competent and friendly cooperation, that I never found anywhere else in the many different research laboratories where I later worked in various countries in my life. Moreover, through Arthur and Joy, I not only forged my professional competence, but also my personal identity as young woman and wife, as I especially loved the warmth and deepness of their familial life, whose spirit I tried to transmit to my own family. In the passing years, I had the fortune and the joy to share with them many moments of happiness and cultural experience, to create true friendship with their children, almost as a spiritual bond and a legacy of love and inspiration for knowledge to be transmitted to future generations.

Dr. Arthur Moss and his wife Joy, 2008.

Products News

Latest Releases

In Q2 2018, we have released:

- A new version of CalECG (v. 4.1.0), Fat-QT (v. 2.1.0) and ECGSolve (v. 2.5.0) with the latest version of BRAVO algorithm (v. 4.7.0) and the new vectorized PDF ECG report.

Looking forward

In Q3 2018, AMPS is planning to release:

- A new version of CER-S (v. 3.2.0.), including the following deeply revised platforms:
  - Continuous ECG beat detection and classification, including a fully renewed ABILE algorithm
  - ECG beat editor with the new editing tools
  - Arrhythmia detection and Arrhythmia editor
  - ECG Beat Measure, for measuring both on beat-to-beat basis and averaged time-templates.

AMPS Notebook

Fabio attended the **43rd ISCE Annual Conference** held in April, where he chaired the last session of the conference "*Session X: Update on International Initiatives and Standards*" and gave the presentation "*Exchange of digital ECGs: do we have enough formats*?"

Later in May, we attended the CSRC, FDA, CipA Meeting: held in Washington, DC. The four components of CiPA collectively seek to characterize more clearly the torsadogenic risk of drugs by providing a more comprehensive assessment of a drug's effect on multiple cardiac ionic currents rather than just hERG. *In vitro* assessment of drug-induced effects on ionic currents focuses primarily on hERG, late sodium, and L-type calcium (calcium) currents. *In silico* computer modeling integrates individual ion channel data to predict the clinical risk of *Torsade*. ECG biomarkers, e.g., the heart rate-corrected J-Tpeak interval (J-Tpeakc), are studied in Phase 1 clinical trials to check for unanticipated effects compared with nonclinical ion channel data and *in silico* modeling predictions.