Figure 1. Fixed-effect meta-regression analyses for the log-odds ratio (ln OR) on mortality (expressed as odds) of the control group at 6- to 12-month follow-up. Negative values of the ln OR (y axis) mean more benefits in mortality associated with abciximab administration, whereas the mortality rate of the control group (x axis) represents the risk profile of the patient population included in each trial. The size of the circle corresponds to the inverse variance of the log-odds ratio, and thus is related to the statistical weight of the study.

mortality. Furthermore, several non-randomized studies have shown significantly better survival in patients with cardiogenic shock treated with primary angioplasty and abciximab (4).

Recent investigations have shown that time to treatment is a relevant issue in primary angioplasty and has a significant impact on mortality (5). Therefore, early administration of pharmacologic therapy may improve earlier reperfusion with subsequent smaller infarct size and better clinical outcome, particularly in high-risk patients and when long-distance transportation is required. In the majority of the trials, abciximab was given just before the angioplasty procedure. Only a few and small randomized trials have been conducted so far to investigate the role of early abciximab administration during transportation. Data from large ongoing randomized trials hopefully will clarify this relevant issue, particularly in high-risk patients.

This meta-analysis shows a direct correlation between the patient's risk profile and the benefits in mortality from abciximab administration as an adjunctive therapy to mechanical revascularization for STEMI. Thus, adjunctive abciximab should be considered in primary angioplasty, particularly in high-risk patients, that may be identified by the use of validated risk scores for STEMI (6).

*Giuseppe De Luca, MD

*Division of Cardiology
Federico II University
Via A. Pansini, 5
80131 Naples
Italy
E-mail: p.de_luca@libero.it

Harry Suryapranata, MD
Gregg W. Stone, MD
David Antoniucci, MD
James E. Tcheng, MD
Franz-Josef Neumann, MD
Erminio Bonizzoni, PhD
Eric J. Topol, MD
Massimo Chiariello, MD

REFERENCES

1. De Luca G, Suryapranata H, Stone GW, et al. Adjunctive abciximab to reperfusion therapy in patients with acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005;193:1759–65.
2. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589–624.
3. Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112–7.
4. Antoniucci D, Valenti R, Migliorini A, et al. Abciximab therapy improves survival in patients with acute myocardial infarction complicated by early cardiogenic shock undergoing coronary artery stent implantation. Am J Cardiol 2002;90:353–7.
5. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time-delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute delay counts. Circulation 2004;109:1223–5.
6. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031–7.

Integrated Backscatter in Becker Muscular Dystrophy Patients With Functionally Normal Heart: Myocardial Ultrasound Tissue Characterization Study

To the Editor: Becker muscular dystrophy (BMD) is an allelic X-linked recessive disorder characterized by an in frame deletion encompassing one or more exons of the dystrophin gene, with a large phenotypic spectrum, ranging between severe childhood-onset muscular disease to asymptomatic cases. Cardiac involvement (leading to cardiomyopathy and heart failure) is frequent, age-dependent, and unpredictable (1). Since there is no direct relationship between severity of skeletal and cardiac involvement, cardiomyopathy frequently develops in patients with normal skeletal muscle function (2).

Recently, we showed that ultrasound tissue characterization (UTC) of myocardium is able to detect widespread signs of cardiac involvement even in Duchenne muscular dystrophy (DMD) chil-dren with normal electrocardiographs (ECGs) and left ventricular systolic function (3). This surprising observation lead to the hypothesis that UTC may be a useful tool in assessing early myocardial involvement in patients with other genetic diseases causing structural changes of myocardium (4). To further explore this hypothesis, we performed UTC analysis in a group of 34 BMD patients with no cardiac symptoms (ages 4 to 33 years, mean 17 ± 10 years), all with normal ECGs, left ventricular diastolic and systolic function, and segmental wall motion at baseline two-dimensional echocardiography, and in 34 healthy age-matched control subjects. The diagnosis of BMD was confirmed by muscular biopsy in all cases. None of the patients was under pharmacological treatment.
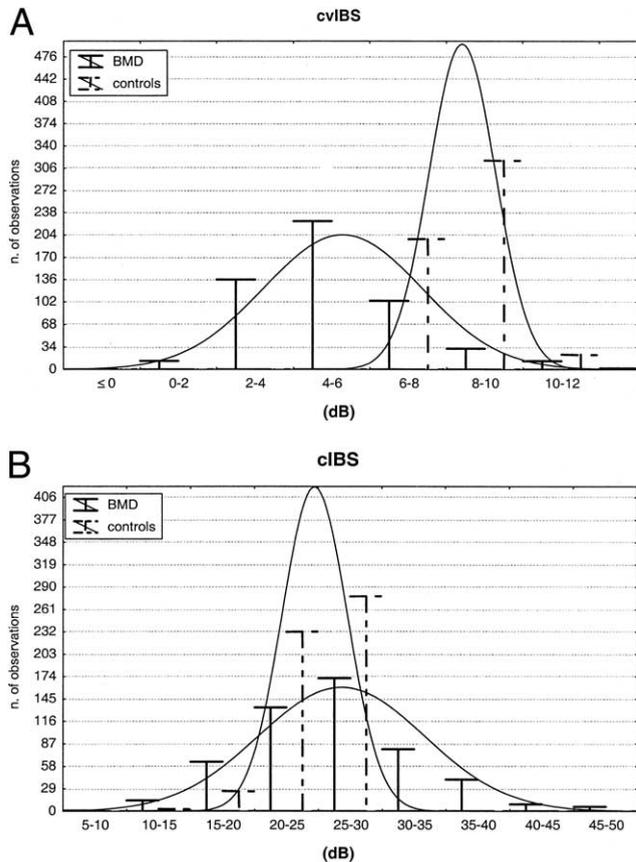
Figure 1. (A) Cyclic variation of integrated backscatter (cvIBS): data distribution in Becker muscular dystrophy (BMD) patients and control subjects. **(B)** Calibrated integrated backscatter (cIBS): data distribution in BMD patients and control subjects.

Ultrasound tissue characterization analysis of the myocardium was performed in the parasternal short-axis view as previously reported (3). In order to obtain a detailed regional analysis of the myocardium, UTC parameters were measured at basal, mid- (papillary muscles), and apical level, in all 16 myocardial segments of the left ventricle, a technique never performed before. All UTC parameters were compared using non-parametric statistics (Mann-Whitney U test and Kruskal-Wallis analysis of variance). Bonferroni correction was applied for multiple comparisons of the same variable (i.e., comparison of UTC parameters in multiple myocardial segments). Correlations were assessed by Spearman's rank correlation test. A value of $p < 0.05$ was considered significant. All values are shown as mean $\pm$ SD.

No significant differences were found in the mean values of ejection fraction and in the mean values of Doppler mitral inflow and annular tissue Doppler imaging velocity between BMD patients and healthy control subjects. Analysis of both cyclic variation of integrated backscatter (cvIBS) and calibrated integrated backscatter (cIBS) was performed on 539 segments in control subjects and on 534 segments in patients, as quality of imaging was inadequate in 5 segments of the control group and in 10 segments of BMD patients.

Overall, BMD patients and control subjects displayed different curves of distribution of cvIBS (mean value of 5.3 ± 2.0 dB vs. 8.4 ± 0.9 dB, $p < 10^{-6}$) (Fig. 1A) and cIBS (mean value of 27.0 ± 6.5 dB vs. 24.7 ± 2.6 dB, $p < 10^{-6}$) (Fig. 1B).

Figure 2 shows a UTC analysis for a patient and a control subject in an inferior base segment.

A comparison of UTC values in each segment showed that BMD patients had significantly lower cvIBS values in all 16 myocardial segments: median 5.2 dB, range 4.4 to 7.0 dB in BMD patients; median 8.3 dB, range 7.9 to 8.7 dB in control subjects ($p < 0.0002$ for all segments); moreover, in all segments SD was larger in BMD patients than in the control group. Conversely, cIBS was significantly different between BMD patients and control subjects only in the inferior, posterolateral base and inferolateral mid-segments from basal through apical levels. In anterior, lateral, and septal segments, cIBS was not significantly different in the two groups, although SD was constantly larger in the BMD group as compared to the control group.

Patients with a deletion of exons 48, 49, or both (n = 15) had lower values of cvIBS as compared to patients with deletions of different exons (n = 19) (4.8 ± 0.6 dB vs. 5.6 ± 0.9 dB, respectively, $p = 0.009$). These two groups had similar cIBS values (27.3 ± 3.2 dB vs. 26.5 ± 4.1 dB, $p = 0.33$). Neither age nor severity of muscular involvement (patients divided into four grades of muscular involvement) were significantly correlated to cvIBS ($r = -0.10$, $p = 0.56$ for age; $r = -0.23$, $p = 0.18$ for severity) or cIBS ($r = 0.08$, $p = 0.64$ for age; $r = 0.22$, $p = 0.22$ for severity) values.

The present study shows that UTC can identify early changes of myocardial physical properties in patients with BMD, even in the absence of left ventricular diastolic and systolic dysfunction.

In BMD patients, differences in the amount of myocardial dystrophin and in the site of the deletion, as well as other still-unidentified factors, are probably the molecular basis of the cardiac involvement that is common in BMD patients, with ECG changes in about 70% of cases (2) and reduced systolic function in up to 60% (1). Since the muscle involvement is often mild and heart disease is a frequent cause of death in BMD (in up to 50% of patients) (5), cardiac transplantation has been successfully performed in these patients. This wide spectrum of genetic background and phenotypic expression is confirmed by the wide range of variation of cvIBS and cIBS in BMD patients, whereas in
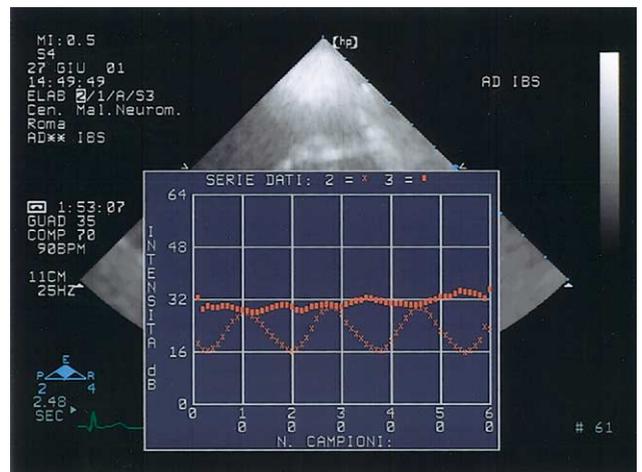

Figure 2. Plot of ultrasound tissue characterization (UTC) sampled on ib (inferior base) segment in a 13-year-old Becker muscular dystrophy (BMD) child with deletion 47-49 **(upper curve)** and in an age-matched healthy control **(lower curve)**. The **bottom curve (control)** has lower calibrated integrated backscatter (cIBS) values, with a clearly wider cyclic variation (cvIBS) compared with the **flat curve** of the BMD patient.

normal control subjects, both parameters are always within a very narrow range in all myocardial segments. Yet, despite this variation, UTC analysis could easily identify widespread changes of myocardial features in BMD patients compared with control subjects. In particular, cvIBS values in BMD patients were markedly different from the control group; no overlap was observed between cvIBS mean values in any of the sampled myocardial segments. Conversely, significant changes in cIBS were detected only in the inferior, posterolateral base and inferolateral mid-segments. These UTC findings in BMD patients as previously described in DMD patients (3) support the hypothesis that myocardial UTC analysis could reveal the early signs of a future evolution toward a segmental myocardial dysfunction.

Furthermore, we found that patients with a deletion encompassing exons 48 and/or 49 had lower values of cvIBS than patients with different or other deletions, possibly suggesting more subtle changes of myocardial physical properties in these patients, in agreement with a previous study suggesting a more frequent cardiac involvement in BMD patients carrying deletions involving exons 48 or 49 (2).

Probably, cvIBS is able to detect a different "cellular milieu" and, finally, early changes of myocardial properties in BMD patients, even in the absence of functional myocardial dysfunction.

Our results show that a myocardial involvement is always present in BMD patients, independent of age, type of deletion, amount of dystrophin in muscle, and severity of skeletal muscle involvement, despite a normal left ventricular diastolic and systolic function.

This paper provides UTC values, in the widest number of myocardial segments ever sampled, in BMD patients with a functionally normal heart.

*Vincenzo Giglio, MD

*Centre for Neuromuscular Diseases, Uildm
Prospero Santacroce St., 5
00167 Rome
Italy
E-mail: giglio.echo@libero.it

Vincenzo Pasceri, MD, PhD, FACC
Loredana Messano, MD
Quintino Parisi, MD
Gabriele Rinelli, MD
Luciano Pasquini, MD
Antonio Dello Russo, MD
Aldo Broccolini, MD, PhD
Giuliana Galluzzi, MD, PhD
Mario Pescatori, MD, PhD
Massimiliano Mirabella, MD
Teresa Gidaro, MD
Fortunato Mangiola, MD
Enzo Ricci, MD

REFERENCES

1. Steare SE, Dubowitz V, Benatar A. Subclinical cardiomyopathy in Becker muscular dystrophy. Br Heart J 1992;68:304–8.
2. Melacini P, Fanin M, Danieli GA, et al. Cardiac involvement in Becker muscular dystrophy. J Am Coll Cardiol 1993;22:1927–34.
3. Giglio V, Pasceri V, Messano L, et al. Ultrasound tissue characterization detects preclinical myocardial structural changes in children affected by Duchenne muscular dystrophy. J Am Coll Cardiol 2003;42: 309–16.
4. Towbin J. A noninvasive means of detecting preclinical cardiomyopathy in Duchenne muscular dystrophy? J Am Coll Cardiol 2003;42:317–8.
5. Finester J, Stollberger C. The heart in human dystrophinopathies. Cardiology 2003;99:1–19.

Letters to the Editor

Link Between Arterial Inflammation and Circadian Rhythm: The Oversight Aspect in the Year 2004

We read with great interest the recent report by Moreno P et al. (1) concerning inflammation as one of the primary pathophysiologic processes in cardiovascular disease. However, we would like to add two comments.

First, it has also been clearly documented that the occurrence of coronary syndromes during the day are not uniform; rather, they occur with rhythmic variation. The existence of a circadian rhythm in the acute coronary syndrome suggests that the problem might, in some way, be associated with, or started by, physiological rhythms, with peak activity at certain parts of the day or night. Numerous studies have tried to establish the cause for this circadian rhythm and its clinical and therapeutic implications (2). Experimental studies have shown that both immune cell number and immune functions may vary during the 24-h circadian period (3).

Second, the increase in mortality from cardiovascular events in winter might be due to alterations in the biological clocks located in the suprachiasmatic nuclei, whose rhythm is determined by day–night alternation, that is, by the light/darkness cycles. These cycles regulate functions such as the secretion of cortisol (4), blood pressure (5), vasomotor tone (6), tissue plasminogen activator (7), and pro-inflammatory cytokines (8,9).

Therefore, considering the potential association among inflammation and circadian rhythm, the presence of a variability during the 24 h of inflammatory and immunologic functions would permit, hypothetically, one to identify the light/dark times in which any peak of inflammatory activity could be associated with a greater incidence of cardiovascular events.

*Alberto Dominguez-Rodriguez, MD, PhD
Martin Garcia-Gonzalez, MD
Pedro Abreu-Gonzalez, MD

*Hospital Universitario de Canarias
Cardiology
Coronary Care Unit
Ofra s/n, La Cuesta
La Laguna,
Tenerife E-38320
Spain
E-mail: adrvdg@hotmail.com