Effects of steroids and angiotensin converting enzyme inhibition on circumferential strain in boys with Duchenne muscular dystrophy: a cross-sectional and longitudinal study utilizing cardiovascular magnetic resonance

Kan N Hor1*, Wojciech Mazur2, Michael D Taylor1, Hussein R Al-Khalidi3, Linda H Cripe1, John L Jefferies1, Subha V Raman4, Eugene S Chung2, Kathi J Kinnett1, Katelyn Williams1, William M Gottliebson1 and D Woodrow Benson1

Abstract

Background: Steroid use has prolonged ambulation in Duchenne muscular dystrophy (DMD) and combined with advances in respiratory care overall management has improved such that cardiac manifestations have become the major cause of death. Unfortunately, there is no consensus for DMD-associated cardiac disease management. Our purpose was to assess effects of steroid use alone or in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) on cardiovascular magnetic resonance (CMR) derived circumferential strain ($\varepsilon_{cc}$).

Methods: We used CMR to assess effects of corticosteroids alone (Group A) or in combination with ACEI or ARB (Group B) on heart rate (HR), left ventricular ejection fraction (LVEF), mass (LVM), end diastolic volume (LVEDV) and circumferential strain ($\varepsilon_{cc}$) in a cohort of 171 DMD patients >5 years of age. Treatment decisions were made independently by physicians at both our institution and referral centers and not based on CMR results.

Results: Patients in Group A (114 studies) were younger than those in Group B (92 studies) (10 ± 2.4 vs. 12.4 ± 3.2 years, p < 0.0001), but HR, LVEF, LVEDV and LVM were not different. Although $\varepsilon_{cc}$ magnitude was lower in Group B than Group A (-13.8 ± 1.9 vs. -12.8 ± 2.0, p = 0.0004), age correction using covariance analysis eliminated this effect. In a subset of patients who underwent serial CMR exams with an inter-study time of ~15 months, $\varepsilon_{cc}$ worsened regardless of treatment group.

Conclusions: These results support the need for prospective clinical trials to identify more effective treatment regimens for DMD associated cardiac disease.

Background

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder affecting approximately 1:3,500 males [1-3]. Boys with DMD are currently treated with corticosteroids at a young age to prolong ambulation. This therapy combined with improvements in respiratory care have resulted in increased survival [4-6] such that DMD-associated heart disease is now the leading cause of mortality [7-11]. Myocardial changes, as a result of the lack of dystrophin, consist of cell membrane degradation, interstitial inflammation, edema, fatty replacement and fibrosis [12-15]. Despite reports in small cohorts of the beneficial cardiovascular effects of corticosteroids [6,16] and angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) [17-19], there is no consensus regarding the management of DMD-associated cardiac disease.
cardiac disease. In the absence of conclusive randomized clinical trial data, steroids, ACEI, ARB, beta blockers (BB) and/or digoxin have been used empirically [20,21]; beneficial effects of positive inotropic agents have been reported in boys with depressed left ventricular function and advanced cardiac disease [22].

Defining clinical endpoints for cardiac therapy in DMD boys is challenging. Recent studies from our center and others have shown that indices of global left ventricular (LV) function, e.g. mass, volume and ejection fraction (EF) are not adequate to detect cardiac dysfunction in young DMD patients [23-25], but myocardial strain ($s$), an indicator of local myocardial deformation normalized to its original dimension, can detect occult cardiac disease early in the course of DMD despite normal EF. Further, depressed $s_{cc}$ magnitude correlates with disease progression [24,25].

The purpose of this study was to retrospectively compare cardiac effects of corticosteroid monotherapy versus corticosteroids plus ACEI or ARB in a cohort of DMD patients followed at our center. We compared effects on both global LV function (EF) and local LV function ($s_{cc}$) determined by cardiovascular magnetic resonance (CMR).

**Methods**

DMD patients >5 years of age who underwent CMR from February 2006 to February 2010 were identified from the CMR database at Cincinnati Children’s Hospital Medical Center (CCHMC). The diagnosis of DMD was confirmed by physical examination and identification of a dystrophin mutation. This study was approved by the Institutional Review Board.

Patients were identified for inclusion in one of two treatment groups. Group A was only treated with corticosteroids (either deflazacort or prednisone). Group B was being treated with corticosteroids plus ACEI (lisinopril or enalapril) or ARB (losartan). All patients in Group B had been treated with corticosteroids plus ACEI or ARB in a cohort of DMD patients followed at our center. We compared effects on both global LV function (EF) and local LV function ($s_{cc}$) determined by CMR database at Cincinnati Children’s Hospital Medical Center (CCHMC).

CMR studies were conducted on either a 3 Tesla (Trio, Siemens Medical Solutions, Erlangen, Germany) or 1.5 Tesla (Signa Excite, General Electric Healthcare, Milwaukeee, WI) scanner based on clinical availability, independent of the patient’s clinical status or prior type or field strength of the first study. Cardiac functional imaging was performed using retrospective ECG-gating, segmented Steady State Free Precession (SSFP) technique after localized shimming and/or frequency adjusting. Subjects were breath-held as tolerated; for those subjects who could not adequately breath-hold, a free breathing technique with multiple signal averaging was used. Standard imaging included a short axis stack of cine SSFP images from cardiac base to apex; the short axis was prescribed as the perpendicular plane to the left ventricular long axis in 2 and 4 chamber views as previously described [26,27]. Typical scan parameters included FOV = 32-38 cm, slice thickness = 5-6 mm, gap = 1-2 mm, NEX = 2 (breath hold; 4-5 for free breathing), TE/TR = 1.4/2.8 (Siemens), TE/TR = 2.0/4.0 (GE), in-plane resolution = 1.2-2.2 mm. A minimum of 12 slices were performed, with 20 phases/slice. The typical temporal resolution of the cine SSFP images was 30-40 ms; they were adjusted according to the patient heart rate and ability to breath-hold. The RF flip angles were set between 50°-70° dependent on the patient weight, height and the SAR level.

Tagged cine CMR images were acquired in the short axis of the midventricle at the level of the papillary muscles using an ECG-triggered segmented k-space fast gradient echo sequence with spatial modulation of magnetization in orthogonal planes. Tag imaging was performed prior to administration of Gadolinium. Grid tag spacing was 7-8 mm. The scan parameters used were: field of view = (30-32) × (25-26) cm², slice thickness = 6 mm, flip = 20°, TE/TR = 3 ms/6.6 ms (GE), = 3 ms/4.2 ms (Siemens), views per segment = 8 (GE), = 7-9 (Siemens). Tagged images were analyzed using the HARmonic Phase (HARP, Diagnosoft, CA, USA) technique [23,28-32]. Only the mid-ventricular slice was analyzed, based on our experience and others’ [23] of limited reproducibility of the basal and apical slices. Details of the $s_{cc}$ analysis have been previously described by Hor et al. [24]. The $s_{cc}$ data was exported to a spreadsheet file for analysis.

Cardiac functional imaging was performed to determine LV volumes, mass and EF using semi-automated endocardial and epicardial segmentation (QMass v.6.1.5, Medis Medical Imaging Systems) Netherlands and circumferential strain ($s_{cc}$) using HARmonic Phase analysis (HARP, Diagnosoft, Palo Alto, California) as previously described [23-25,29-31,33-35].

Results are expressed as mean ± SD for continuous data and as percentages and numbers for categorical data. Continuous variables were compared using two-sample t-test and categorical variables were compared using Fisher exact-test. Analysis of covariance (ANCOVA) was used to assess the effect of medications on several clinical measurements with age as a continuous covariate in the model. All tests were 2-sided, and a $p$-value < 0.05 was considered statistically significant. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.
Results
We identified 171 DMD patients > 5 years of age that had undergone CMR examination. A total of 256 studies were available for review as a number of patients had multiple studies. We excluded 50 studies for either no corticosteroid treatment at the time of study (36 studies) or treatment with beta-blockers at the time of study (14 studies). The remaining 206 studies from 136 patients were divided into two groups: Group A (corticosteroids alone, n = 114) and Group B (corticosteroids plus ACEI or ARB, n = 92). Group A patients were significantly (p < 0.0001) younger (10 ± 2.4 years) than Group B patients (12.4 ± 3.2 years).

The average steroid dose was similar between Group A and Group B (0.7 ± 0.29 mg/kg/day, range 0.1-1.9 vs. 0.6 ± 0.22 mg/kg/day, range 0.1 - 1.3, p = 0.48). The patients in Group B were on standard dose of ACEI (0.16 ± 0.29 mg/kg/day, range 0.04 - 1.23) and ARB (0.73 ± 0.29 mg/kg/day, range 0.34 - 1.23) (Table 1).

Heart rate, LV EF, LV end diastolic volume (LVEDV) and LV mass (LVM) were not different between the two groups. LVEF averaged across all patients in this cohort was normal, but ε_{cc} magnitude was significantly lower in Group B (-12.8 ± 2) versus Group A patients (-13.8 ± 1.9, p = 0.0004). To determine the extent to which differences in the two groups was an effect of patient age, we performed a covariance analysis and treated age as a continuous variable (Table 2). The covariance model confirmed the lack of significant differences between Groups A and B with respect to heart rate, EF, LVEDV, LVM, LVRI or ε_{cc} after controlling for age, implying lack of difference between the two groups other than the use of cardiac medications in Group B.

Additionally, to assess serial changes in EF and ε_{cc}, we identified patients in Group A (n = 28) and B (n = 31) who underwent 2 CMR studies during the observation period. This included 11 patients who crossed from Group A to B between sequential studies. Among individuals with 2 studies, EF and ε_{cc} values were compared between the two studies (Figure 1). EF changes between the first and second study were variable across three groups, while the majority of patients had decline in ε_{cc} magnitude over the same study period. In Group A, 50% (14/28) patients had decrease EF while the other 50% (14/28) had increase EF. Of Group A patients, 7% (2/28) had changes in EF by > 10%, however one increased by almost 15% and the other decrease by 12%. Both patients continue to have normal EF (>55%) on both studies. One patient had EF < 55% on the first study which remained the same on the second study and another patient had EF that decline from 59% to 54%. However, only 14% (4/28) of Group A subjects had an increase ε_{cc} magnitude while 86% (24/28) had worsening of ε_{cc} magnitude. The findings for Group B were similar, with 68% (21/31) of patients having decrease EF and 32% (10/31) of patients with increase EF over the two study. Of Group B patients, 28% (9/32) had changes in EF by > 10% with 6 patients having decrease EF and 3 patients with increase EF on the follow-up study. Of these, One patient started with an EF of 53% and increased to 64% on the follow-up study. Of the 6 patients with decrease in EF, three had EF < 55% while the other three continue to have normal EF on the follow-up study. As in Group A, 84% (26/31) of the Group B patients had decrease ε_{cc}, while only 16% (5/31) subjects showed improvement in ε_{cc} magnitude. For the patients that crossed from Group A to B, the percent of patients with improved EF was 45% (5/11) while 55% (6/11) had decline in EF. The percent of patients with an increase in ε_{cc} magnitude was 18% (2/11) but 82% (9/11) had worsening of ε_{cc} magnitude (Figure 1). The average time between studies was the same across Group A, Group B and patients who transitioned from Group A to B. LVEF did not change significantly between baseline and follow-up in all three groups (Table 3). While ε_{cc} worsened from initial to follow-up CMR exam in all three groups, reduction in ε_{cc} only reached statistical significance in Group B (Table 3).

### Table 1 DMD Patients characteristics

| Parameter      | Steroid Only (A)(n = 114) | Steroid plus ACEI_ARB (B)(n = 92) | P-value |
|----------------|---------------------------|----------------------------------|---------|
| Age (yrs)      | 10.0 ± 2.4                | 12.4 ± 3.2                       | <0.0001 |
| Heart Rate (bpm)| 101 ± 19                  | 104 ± 15                        | 0.2498  |
| LVEDV (mL)     | 82.5 ± 21.8               | 86.7 ± 24.8                     | 0.0203  |
| LVM (g)        | 58.6 ± 19.4               | 62.1 ± 19.8                     | 0.1031  |
| EF (%)         | 64.2 ± 6.1                | 62.8 ± 7.5                      | 0.1414  |
| ε_{cc} (%)     | -13.8 ± 1.9               | -12.8 ± 2.0                     | 0.0004  |
| Steroid dose (gram/kg/day) | 0.7 ± 0.29             | 0.6 ± 0.22                      | 0.4838  |
| ACE-I dose (gram/kg/day)      | N/A                       | 0.16 ± 0.08                     | N/A     |
| ARB dose (gram/kg/day)        | N/A                       | 0.73 ± 0.29                     | N/A     |

Abbreviations: ACE-I = Angiotension Converting Enzyme Inhibitor, ARB = Angiotension Receptor Blocker, bpm = beat per minute, Clinic Prior to CMR = Previous Clinic Visit Documenting Medication and Dose Prior to Cardiac Magnetic Resonance Imaging Study, DMD = Duchenne Muscular Dystrophy, ε_{cc} = Circumferential Strain, EF = Ejection Fraction, LVEDV = Left Ventricular Endiastolic Volume, LVM = Left Ventricular Mass.
Discussion

This study represents the largest cohort of DMD patients analyzed for the effect of medical therapy on the natural history of DMD-associated cardiac disease. Albeit retrospective, these results suggest that treatment with either an ACEI or ARB does not arrest the decline in DMD-associated cardiac function in patients receiving corticosteroids. In fact, we found a statistically significant worsening in $\varepsilon_{cc}$ in patients taking both corticosteroids and ACEI or ARB, suggesting that current approaches are inadequate in arresting decline in cardiac function.

Clinical assessment of DMD-associated cardiac disease is particularly challenging, as overt decompensation typically occurs only in the terminal stages of disease at a time when clinical assessment of cardiac function is limited. A sensitive and specific parameter such as $\varepsilon_{cc}$ could thus assume great importance in management of these patients. Previous studies have shown that changes in $\varepsilon_{cc}$ precede decline in LVEF in DMD-associated cardiac disease as well as in both hypertrophic and hypertensive cardiomyopathy [24,36-38]. Using such an early marker of subclinical disease in a cohort with preserved LVEF, we were unable to detect an improvement with standard therapies.

Assessment of cardiac effects of corticosteroid therapy in animal models and patients has historically yielded mixed results. For example, corticosteroids have been shown to improve systolic function in children with myocarditis but...
Table 3 Results from Serial CMR Exams Across DMD Treatment Groups

| CMR Study | Study 1 | Study 2 | P-value | Study 1 | Study 2 | P-value | Study 1 | Study 2 | P-value |
|-----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Age (yrs) | 9.30 ± 1.5 | 10.5 ± 1.6 | <0.005 | 11.7 ± 3.4 | 12.97 ± 3.4 | 0.148 | 10.8 ± 2.5 | 12.0 ± 2.2 | 0.252 |
| HR (bpm)  | 101 ± 21 | 99 ± 16 | 0.762 | 105 ± 14 | 105 ± 15 | 0.996 | 100 ± 14 | 102 ± 18 | 0.682 |
| LVEDV (mL)| 82.7 ± 19.3 | 86.5 ± 21.6 | 0.494 | 84.9 ± 29.2 | 90.0 ± 30.8 | 0.499 | 85.6 ± 18.6 | 81.2 ± 15.6 | 0.556 |
| LVM (g)   | 57.1 ± 15.1 | 57.7 ± 16.9 | 0.890 | 60.9 ± 21.4 | 65.0 ± 21.4 | 0.478 | 61.3 ± 31.2 | 60.1 ± 14.0 | 0.909 |
| EF (%)    | 64.6 ± 6.3 | 64.4 ± 5.8 | 0.906 | 64.9 ± 6.7 | 62.2 ± 9.1 | 0.194 | 61.2 ± 5.0 | 63.8 ± 5.8 | 0.261 |
| ε_{cc} (%)| -14.3 ± 1.6 | -13.7 ± 1.5 | 0.135 | -13.4 ± 1.7 | -12.1 ± 1.6 | 0.007 | -13.2 ± 1.8 | -11.9 ± 2.7 | 0.179 |

Abbreviations: BMP = beat per minute, DMD = Duchenne Muscular Dystrophy, ε_{cc} = Circumferential Strain, EF = Ejection Fraction, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HR = heart rate, LVEDV = Left Ventricular Endiastolic Volume (milliliter), LVM = Left Ventricular Mass (gram).
not with dilated cardiomyopathy [39]. Markham et al demonstrated that freedom from ventricular dysfunction at approximately 50 months between retrospectively-reviewed echocardiograms was 93% for steroid treated versus 53% for untreated DMD cases [6]. However, in a mouse model of dystrophin deficiency, Bauer et al demonstrated acceleration of cardiac dysfunction in steroid treated animals [40]. Recently, Pereira et al [41] observed normalization of multidirectional (radial, longitudinal and circumferential) strain assessed by 2D echo speckle tracking in Cushing syndrome patients following normalization of corticosteroid excess; they concluded that corticosteroid excess not only induced LV hypertrophy and diastolic dysfunction but also subclinical systolic dysfunction, which reverses upon normalization of corticosteroid excess. While there is universal agreement that steroids prolong ambulation in the DMD patient population (reviewed in [21]), the current study failed to identify a cardioprotective effect of steroids.

Several studies have suggested beneficial effects of ACEI on LV function in small cohorts [17-19,42]. In a murine DMD model, Bauer et al showed hemodynamic benefit to dystrophin-deficient mice treated with ACEI alone [40]. Jefferies et al suggested that this effect may be linked to specific mutations [19] in humans, but Ramaciotti et al [42] did not confirm this finding. In addition to $\varepsilon_{cc}$, we found no difference in EF between baseline and 15 months, which is at odds with the findings of Duboc et al [17] who found that treatment with perindopril delayed the onset and progression of LV dysfunction in children. There are several possible explanations for the differences in findings. First, in our cohort, the time between the serial CMR studies might be insufficient to develop detectable LV EF decline. However, one would expect to detect more subclinical changes using the more sensitive measure LV $\varepsilon_{cc}$. Furthermore, without an untreated control group, the fact that $\varepsilon_{cc}$ magnitude declined only slightly may represent a “good” outcome, as LV function of untreated patients may decline more precipitously. Despite smaller studies reporting benefit of ACEI and BB, there is no published data demonstrating longer life expectancy in DMD boys undergoing “adult-like” CHF therapy.

A long-standing hypothesis regarding DMD-associated cardiac disease pathogenesis is that loss of membrane integrity is a primary event leading to myocyte degeneration. Intermittent tears in the cell membrane permit influx of calcium that then functions as a primary inducer of a destructive cascade culminating in myocyte necrosis and replacement fibrosis [43]. Although there has been intense interest in treating DMD-associated cardiac disease, successful therapies remain elusive [22,44-46]. Findings in the current study underscore the need for randomized studies in DMD population. As in cases of heart failure in adult population, development of heart failure with normal EF starts early (HFNEF) and proceeds to systolic dysfunction. Of interest, studies in adult HFNEF patients treated with ACEI or BB have not demonstrated improvement in mortality compared to placebo [47-49]. In boys with DMD, dystrophin mutation dictates eventual LV dysfunction and once systolic dysfunction and myocardial fibrosis develop, clinical disease typically progresses very rapidly and long-term survival (as seen in adult patients with LV systolic dysfunction) is poor. As such, the window of opportunity to treat DMD-associated cardiac disease needs to be advanced to when $\varepsilon_{cc}$ is abnormal but EF has not yet begun its inexorable declined.

Study Limitations
Study design based on physician preference is a major limitation of the study and includes retrospective, mostly cross-sectional data with no control group and with strong confounding of group allocation by age of boys being prescribed therapy. Older boys tended to be on combination treatment while younger boys were often treated with steroids alone. Further, longitudinal data is limited. Other confounding factors are very difficult to control for but are beyond the scope of this manuscript. As such, no firm conclusions can be drawn regarding the response rates to steroid or ACEI/ARB use. Further, findings are limited to patients >5 years since in our experience patients < 5 years of age cannot undergo CMR without sedation. While it is possible, that 15 months follow-up was too short to detect therapeutic benefits, studies in other populations with preserved EF but measurable diastolic dysfunction have shown improvement in circumferential and longitudinal strain 12 months after ARB initiation [50].

Conclusions
These results support the need for rigorous, prospective clinical trials to identify more effective treatment regimens for DMD-associated cardiac disease.

List of Abbreviations
ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; BB: Beta blockers; bpm: beat per minute; Clinic Prior to CMR: Previous Clinic Visit Documenting Medication and Dose Prior to CMR; CMR: Cardiovascular Magnetic Resonance; DMD: Duchenne Muscular Dystrophy; $\varepsilon_{cc}$: Circumferential Strain; EF: Ejection Fraction; Group A: Steroid only; Group B: Steroid plus; HR: heart rate; LV: Left Ventricular; LVEDV: Left Ventricular Enddiastolic Volume; LVM: Left Ventricular Mass; MO: months.

Acknowledgements and Funding
This work is dedicated to the memory of William M. Gottliebson, MD. Supported in part by the Children’s Heart Association of Cincinnati (WMG) and the National Institutes of Health HL069712 (DWB) Bethesda, MD.

Author details
1The Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, USA. 2The Heart and Vascular Center at The Christ Hospitals, Cincinnati,
Ohio, USA. 2Duke University School of Medicine, Durham, North Carolina, USA. 3The Ohio State University, Columbus, Ohio, USA.

**Authors’ contributions**

KWH and DWB contributed to all aspects of the manuscript’s conception, design, data analysis, collection, critical revision and final approval. HRA, contributed to statistical analysis, revision and final approval. MDT, LHC, JLJ, SVR, ESC, KJH, KW and WMG* contributed in interpretation of the data, critical revision and final approval of the manuscript. All authors have read and approved the final manuscript.

*WKG passed on September 17, 2010 and therefore, did not have the opportunity to give final approval of the manuscript but contributed significantly to it.

**Competing interests**

The authors declare that they have no competing interests.

**Received:** 18 March 2011  **Accepted:** 19 October 2011  **Published:** 19 October 2011

**References**

1. Hoffman EP, Brown RH, Kunkel LM: Dystrophin: the protein product of the Duchenne muscular dystrophy locus. 1987, Biotechnology 1992, 24:457-466.

2. Kunkel LM, Monaco AP, Middleworth W, Ochs HD, Latt SA: Specific cloning of DNA fragments absent from the DNA of a male patient with an X chromosome deletion. Proc Natl Acad Sci USA 1985, 82:4778-4782.

3. Ray PN, Belfall B, Duff C, Logan C, Kean V, Thompson MW, Sylvester JE, Claudio P, Marion A, Jaffe P, Frohlich ED, et al: Clinical and echocardiographic evaluation of 30 patients with Duchenne muscular dystrophy. Eur J Pediatr 1990, 149:173-77.

4. Bushby K, Muntoni F, Urtizberea A, Hughes R, Griggs R: Cardiac manifestation of progressive muscular dystrophies. J Pediatr 2005, 146:772-779.

5. Finder JD, Birnkrant D, Carl J, Farber HJ, Gozal D, Iannaccone ST, Kovesi T, Loukas A, Markham LW, McDonald C, et al: Diagnosis and management of Duchenne muscular dystrophy, part 1: presentation and natural history. J Child Neurol 2005, 20:116-28.

6. Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH: Steroid therapy and cardiac function in Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med 2004, 170:456-465.

7. Markham LW, Spicer RL, Khouy PR, Wong BL, Mathews KD, Cripe LH: Cardiac contractile reserve diagnosed by dobutamine stress echocardiography in a patient with Duchenne muscular dystrophy. J Am Soc Echocardiogr 2006, 19:865-871.

8. Markham LW, Spicer RL, Cripe LH: Heart failure in Duchenne muscular dystrophy. Pediatr Ann 2005, 34:331-335.

9. Wong BL, Mukkada VA, Markham LW, Cripe LH: Depressed left ventricular contractile reserve diagnosed by dobutamine stress echocardiography in a patient with Duchenne muscular dystrophy. J Child Neurol 2005, 20:246-248.

10. Fong PY, Turner PR, Denectalw VF, Steinhardt RA: Increased activity of calcium leak channels in myotubes of Duchenne human and mdx mouse origin. Science 1990, 250:673-676.

11. Morritch T, Kagawa N, Mukayama M, Hizawa K: Autopsy analyses of the muscular dystrophies. Tokushima J Exp Med 1993, 40:33-93.

12. Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT, Pack N, Dibella E, Gottliebson WM: Late gadolinium enhancement: precursor to cardiac myopathy in Duchenne muscular dystrophy? Int J Cardiovasc Imaging 2009, 25:57-63.

13. Silva MC, Meira ZM, Garipel Giannetti J, da Silva MM, Campos AF, Barbosa Mde M, Starling Filho GM, Ferreira Rde A, Zat M, Rochitte CE: Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. J Am Coll Cardiol 2007, 49:1874-1879.

14. Markham LW, Kinnett K, Wong BL, Woodrow Benson D, Cripe LH: Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. NeuroMuscul Disord 2008, 18:365-370.

15. Duboc D, Meune C, Lenebours G, Devaux JY, Yakomann G, Becane HM: Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol 2005, 45:855-857.

16. Duboc D, Meune C, Piere B, Wahbi K, Eymard B, Touitou A, Berard C, Yakomann G, Weber S, Becane HM: Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years’ follow-up. Am Heart J 2007, 154:596-602.

17. Jefferies JL, Edeani RW, Belmont JW, Craigen WJ, Ware SM, Fambard SD, Neish SR, Smith EO, Toivin JA: Genetic predictors and remodeling of diastolic cardiomyopathy in muscular dystrophy. Circulation 2005, 112:2799-2804.

18. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, et al: Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol 2010, 9:177-189.

19. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, et al: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychological management. Lancet Neurol 2010, 9:7-19.

20. Cripe LH, Barber BJ, Spicer RL, Wong BL, Weidner N, Benson DW, Markham LW: Outpatient continuous inotrope infusion as an adjunct to heart failure therapy in Duchenne muscular dystrophy. NeuroMuscul Disord 2006, 16:745-748.

21. Ashford MW Jr, Liu W, Lin SJ, Abrasiveslo P, Caruthers SD, Connolly AM, Yu X, Wickline SA: Occult cardiac contractile dysfunction in dystrophin-deficient children revealed by cardiac magnetic resonance strain imaging. Circulation 2005, 112:2462-2467.

22. Hor KN, Wansapura J, Markham LW, Mazur W, Cripe LH, Fleck R, Benson DW, Gottliebson WM: Circumferential strain analysis identifies strata of cardiomyopathy in Duchenne muscular dystrophy: a cardiac magnetic resonance tagging study. J Am Coll Cardiol 2009, 53:1204-1210.

23. Hagenbuch SC, Gottliebson WM, Wansapura J, Mazur W, Fleck R, Benson DW, Hor KH: Detection of progressive cardiac dysfunction by serial evaluation of circumferential strain in patients with Duchenne muscular dystrophy. Am J Cardiol 2010, 105:1451-1455.

24. Pennell DJ, Sechtem UP, Higgins CW, Manning WJ, Pohost GM, Rademakers FE, van Rossum AC, Shaw LJ, Yucel EK: Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Heart J 2004, 25:1940-1965.

25. Pohost GM, Hung L, Doyle M: Clinical use of cardiovascular magnetic resonance. Circulation 2003, 108:647-653.

26. Gottle MJ, Germans T, Russel K, Zwanenburg JJ, Marcus JT, van Rossum AC, van Veldhuizen AJ: Myocardial strain and torsion quantified by cardiovascular magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. J Am Coll Cardiol 2006, 48:2002-2011.

27. Osman NF, Kerwin WS, McVeigh ER, Prince JL: Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. Magn Reson Med 1999, 42:1048-1060.

28. Osman NF, McVeigh ER, Prince JL: Imaging heart motion using harmonic phase MRI. IEEE Trans Med Imaging 2000, 19:186-202.

29. Osman NF, Prince JL: Regenerating MR tagged images using harmonic phase (HARP) methods. IEEE Trans Biomed Eng 2004, 51:1428-1433.

30. Garot J, Bleumke DA, Osman NF, Rochitte CE, McVeigh ER, Zehouani EA, Prince JL, Lima JA: Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. Circulation 2000, 101:981-988.

31. van der Geest RJ, Reiber JH: Quantification in cardiac MRI. Magn Reson Imaging 1999, 17:602-608.

32. Osman NF, Sampath S, Atalar E, Prince JL: Imaging longitudinal cardiac strain on short-axis images using strain-encoded MRI. Magn Reson Med 2001, 46:324-334.

33. Osman NF, Prince JL: Visualizing myocardial function using HARP MRI. Phys Med Biol 2000, 45:1665-1682.

34. Ennis DB, Epstein FH, Kellman P, Fananapazir L, McVeigh ER, Arai AE: Assessment of regional systolic and diastolic dysfunction in familial

http://www.jcmr-online.com/content/13/1/60
hypertrophic cardiomyopathy using MR tagging. Magn Reson Med 2003, 50:638-642.

37. Rosen BD, Saad MF, Shea S, Nasir K, Edwardsen T, Burke G, Jerosch-Herold M, Arnett DK, Lai S, Buerman DA, Lima JA: Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic individuals the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2006, 47:1150-1158.

38. Young AA, Kramer CM, Ferrari VA, Axel L, Reichek N: Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. Circulation 1994, 90:854-867.

39. Gagliardi MG, Bevilacqua M, Bassano C, Leonardi B, Boldrini R, Camassei FD, Fierabracci A, Ugazio AG, Bottazzo GF: Long term follow up of children with myocarditis treated by immunosuppression and of children with dilated cardiomyopathy. Heart 2004, 90:1167-1171.

40. Bauer R, Straub V, Blin A, Bushby K, MacGowan GA: Contrasting effects of steroids and angiotensin-converting-enzyme inhibitors in a mouse model of dystrophin-deficient cardiomyopathy. Eur J Heart Fail 2009, 11:463-471.

41. Pereira AM, Delgado V, Romijn JA, Smit JW, Bax JJ, Feelders RA: Cardiac dysfunction is reversed upon successful treatment of Cushing’s syndrome. Eur J Endocrinol 2010, 162:331-340.

42. Ramacciotti C, Heisten LC, Coursey M, Lemler MS, Aspen RS, Iannaccone ST, Scott WA: Left ventricular function and response to enalapril in patients with duchenne muscular dystrophy during the second decade of life. Am J Cardiol 2006, 98:825-827.

43. Millay DP, Goonasekera SA, Sargent MA, Maillet M, Aronow BJ, Molkentin JD: Calcium influx is sufficient to induce muscular dystrophy through a TRPC-dependent mechanism. Proc Natl Acad Sci USA 2009, 106:19023-19028.

44. Shaddy RE, Tani LY, Gidding SS, Pahl E, Orsmond GS, Gilbert EM, Lemes V: Beta-blocker treatment of dilated cardiomyopathy with congestive heart failure in children: a multi-institutional experience. J Heart Lung Transplant 1999, 18:269-274.

45. Rhodes J, Margossian R, Dantas BT, Colan SD, Jenkins KJ, Geva T, Powell AJ: Safety and efficacy of carvedilol therapy for patients with dilated cardiomyopathy secondary to muscular dystrophy. Pediatr Cardiol 2008, 29:43-51.

46. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, et al: Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007, 298:1171-1179.

47. Blanche C, Fumeaux T, Polikar R: Heart failure with normal ejection fraction (HFNEF): is it worth considering? Swiss Med Wkly 2010, 140:66-72.

48. Burkhoff D, Maurer MS, Packer M: Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? Circulation 2003, 107:656-658.

49. Hamdani N, Paulus WJ, van Heerebeek L, Borbély A, Boontje NM, Zuidwijk MJ, Bronzwaer JG, Simonides WS, Niesen HW, Stienen GJ, van der Velden J: Distinct myocardial effects of beta-blocker therapy in heart failure with normal and reduced left ventricular ejection fraction. Eur J Heart J 2009, 30:1863-1872.

50. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T: Telmisartan improves morphologic and functional changes in both left ventricular myocardium and carotid arterial wall in patients with hypertension: assessment by tissue Doppler imaging and carotid ultrasonography. Echocardiography 2010, 27:864-872.

doi:10.1186/1532-429X-13-60
Cite this article as: Hor et al: Effects of steroids and angiotensin converting enzyme inhibition on circumferential strain in boys with Duchenne muscular dystrophy: a cross-sectional and longitudinal study utilizing cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance 2011 13:60