

Hutchinson-Gilford Progeria Syndrome and Severe Aortic Stenosis: A New Hope for Treatment

03 **Francesco Musumeci**, MD,
Antonio Giovanni Cammardella, MD, **Antonio Lio**, MD,
Carmine Musto, MD, **Vincenzo Polizzi**, MD,
Vitaliano Buffa, MD, **Andrea Montalto**, MD,
Marina Comisso, MD, **Federico Ranocchi**, MD, and
Mauro Cassese, MD

Department of Cardiac Surgery and Heart Transplantation, San Camillo-Forlanini Hospital, Rome, Italy; Interventional Cardiology Unit, San Camillo-Forlanini Hospital, Rome, Italy; Cardio-Vascular Radiology Unit, San Camillo-Forlanini Hospital, Rome, Italy; and Department of Cardiac Surgery, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Hutchinson-Gilford progeria syndrome is an autosomal dominant, rare, fatal pediatric segmental premature aging disease. Cardiovascular and cerebrovascular diseases constitute the major cause of morbidity and mortality. Patients with the syndrome and severe aortic valve stenosis have been described in the literature, and for all of them a strategy of conservative management has been followed. We describe the first successful treatment of a 23-year-old Hutchinson-Gilford progeria syndrome patient with severe aortic stenosis who underwent transcatheter aortic valve replacement.

(Ann Thorac Surg 2020;■:e■-■)

© 2020 by The Society of Thoracic Surgeons

Hutchinson-Gilford progeria syndrome (HGPS) is an autosomal dominant, fatal pediatric segmental premature aging disease (Figure 1).¹ Cardiovascular and cerebrovascular diseases constitute the major cause of morbidity and mortality.² Cases of HGPS patients with severe aortic stenosis have been described in the literature, but in all of them, a conservative management was followed.^{3,4} We describe the first successful treatment of a HGPS patient with severe aortic stenosis who underwent transcatheter aortic valve replacement.

In January 2019, a 23-year-old man with HGPS was referred to our institution for a severe aortic stenosis. The patient's weight was 20 kg and his height was 1.36 m (body mass index 9.5 kg/m²). The patient, because of his clinical features, was considered to be inoperable. He underwent a two-dimensional and three-dimensional echocardiographic examination that showed an aortic mean gradient of 51 mm Hg and a three-dimensional planimetric area of 0.6 cm² (Video 1). The left ventricle ejection fraction was 65%, confirmed by magnetic reso-

nance imaging scan. The left and right aortic cusps were heavily calcified and rigid, whereas the noncoronary cusp was slightly mobile and 8 mm in length.

The patient then underwent a computed tomography scan study to evaluate the technical feasibility of transcatheter aortic valve replacement. The aortic valve was confirmed to be extensively calcified with calcification extending into the left ventricle outflow tract. The heights of the coronary arteries ostia were 5 mm for the left and 8 mm for the right. The sinotubular junction and ascending aorta diameters were of 19 mm and 23 mm, respectively. The study of coronary arteries by computed tomography scan showed no significant lesions (Figure 2). The iliac diameters were 3.5 mm to 4 mm bilaterally.

The main critical points for the valve replacement procedure were considered the following: (1) the extensive calcification of the aortic valve and left ventricle outflow tract; (2) the very low position of the coronaries ostia, especially the left one; and (3) the tissue frailty that characterizes the progeria disease. The decision was made to proceed with transcatheter aortic valve replacement using a transapical approach owing to the small caliber of the iliac-femoral axis and the severe hip ankyloses. It was also decided to "protect" the left coronary ostia by placing inside the coronary artery an undilated stent, ready to be opened if occlusion occurred as result of the implantation of the aortic valve prosthesis. The Sapien 3 Ultra 20 mm (Edwards Lifesciences, Irvine, CA) was considered to be the most appropriate transcatheter valve to be used in this specific anatomic setting because of an increased outer skirt height and a textured PET material compared with the Sapien 3 or the Sapien XT, and therefore with the potential for better sealing power with a reduced risk of paravalvular leakage.

A left submammary thoracotomy of approximately 4 cm was then performed to expose the cardiac apex, and a pacemaker lead was inserted into the right ventricle through the left femoral vein. Coronary angiography was performed and showed a left coronary artery without significant stenosis; then, an extra backup 3.5 6F balance middleweight universal guidewire was advanced into the left anterior descending artery down to its distal tract, and a 3.5 × 15 drug-eluting stent was positioned in the distal left main artery but not expanded (Video 2).

At this point, the valve prosthesis was positioned across the native aortic valve and the Sapien 3 Ultra 20 mm valve was implanted (Video 3). Consideration was taken of the low position of the left coronary ostium, and therefore the aortic valve prosthesis was implanted in a lower position

Dr Cassese discloses a financial relationship with Edwards Lifesciences.

The Videos can be viewed in the online version of this article [https://doi.org/10.1016/j.athoracsur.2020.03.067] on http://www.annalsthoracicsurgery.org.

Accepted for publication Mar 22, 2020.

Address correspondence to Dr Musumeci, San Camillo-Forlanini Hospital, via Gianicolense 87, Rome 00152, Italy; email: fr.musumeci@gmail.com.



Figure 1. Patient affected by progeria.

than usual. At the end of the procedure, coronary angiography showed normal perfusion of both coronary arteries (Figure 3; Video 4). The unexpanded stent and the guiding catheter were then removed. Transesophageal echocardiography showed absence of paravalvular leakage and a mean gradient of 9 mm Hg.

The patient's postoperative course was totally uneventful and he was discharged to home on the eighth day in good condition; pre-discharge echocardiography confirmed a mean gradient of 11 mm Hg, absence of paravalvular leakage, and no significant pericardial effusion. At 10-month follow-up, the patient was in New York Heart Association functional class I. The echocardiography showed an aortic mean gradient of 16 mm Hg and no



Figure 3. Left coronary angiography after transcatheter aortic valve replacement.

significant paravalvular leakage, with preserved left ventricle ejection fraction.

Comment

Hutchinson-Gilford progeria syndrome is a progressive degenerative disorder with an estimated incidence of one in four million births, and therefore 300 to 350 children

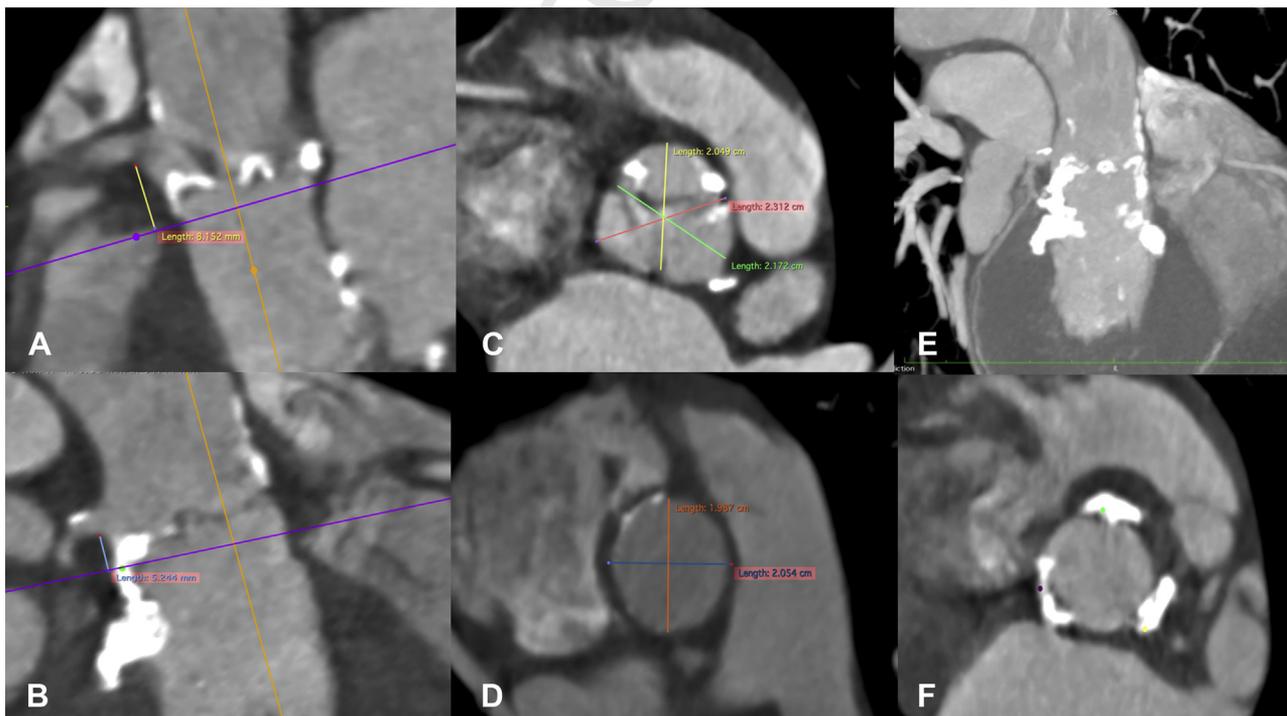


Figure 2. Computed tomography scan: (A) right coronary ostium height; (B) left main ostium height; (C) intercommissural distance; (D) sino-tubular junction; (E) bulky calcification in left ventricle outflow tract; and (F) virtual basal ring.

were estimated to be living with progeria worldwide in 2014. The estimated and average lifespan is 14.6 years.⁵

The mutation causing HGPS is located in the chromosome 1, on the *LMNA* gene.^{6,7} The mutated allele produces an aberrant form of lamin A called progerin. The accumulation of the progerin in the nuclear envelope of the cells causes several symptoms in the body, the most serious ones are in the cardiovascular system: HGPS patients can rapidly develop stiffness in the blood vessels (especially the carotids and the brain arteries), calcification of the heart valves (especially the aortic one), and coronary artery diseases.² Mortality is, indeed, primarily due to myocardial infarction, strokes, or congestive cardiac failure between the ages of 7 and 21 years.^{2,3,8} No effective therapy is currently approved, even if some experimental drugs are undergoing trials. Owing to the high risk-profile of HGPS patients, aortic stenosis has been always managed conservatively.^{3,4}

We have described the first case of successful treatment of a HGPS patient with severe aortic stenosis. Standard surgical aortic valve replacement was considered to be a very high risk procedure, and therefore transcatheter aortic valve replacement was selected as a treatment option. Owing to the small vessel diameter in the peripheral vasculature, a transfemoral approach was not feasible, and a transapical access was used. A multidisciplinary team was involved in the decision-making process as well as in the execution of the procedure.

In conclusion, severe stenosis of the aortic valve is one of the predominant causes of death among HGPS patients but has never been treated owing to the complexity

of this pathology and the high-risk profile of these patients. We have demonstrated that, with the diagnostic and therapeutic technologies available today, in patients with HGPS treatment of a severely stenotic aortic valve is feasible, and it could enhance life expectancy in these patients.

References

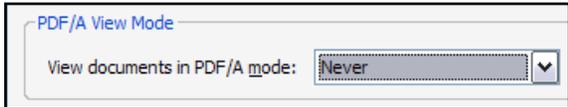
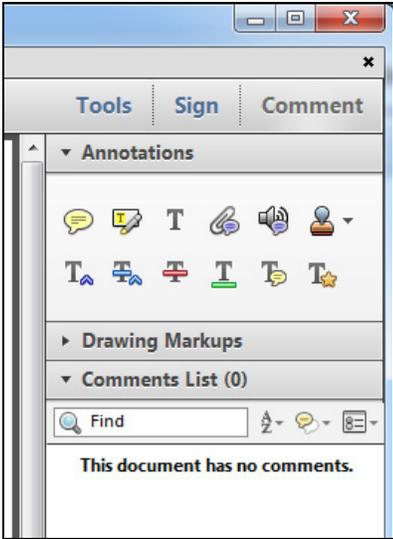
1. Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford progeria syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al. eds. *GeneReviews*. Seattle, WA: University of Washington. 1993.
2. Merideth MA, Gordon LB, Clauss S, et al. Phenotype and course of Hutchinson-Gilford progeria syndrome. *N Engl J Med*. 2008;358:592-604.
3. Nair K, Ramachandran P, Krishnamoorthy KM, et al. Hutchinson-Gilford progeria syndrome with severe calcific aortic valve stenosis and calcific mitral valve. *J Heart Valve Dis*. 2004;13:66-69.
4. Hanumanthappa NB, Madhusudan G, Mahimarangaiah J, Manjunath CN. Hutchinson-Gilford progeria syndrome with severe calcific aortic valve stenosis. *Ann Pediatr Cardiol*. 2011;4:204-206.
5. Gordon LB, Massaro J, D'Agostino RB, et al. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. *Circulation*. 2014;130:27-34.
6. De Sandre-Giovannoli A, Bernard R, Cau P, et al. Lamin A truncation in Hutchinson-Gilford progeria. *Science*. 2003;300:2055.
7. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. 2003;423:293-298.
8. Makous N, Friedman S, Yakovac W, Maris EP. Report of clinical and pathologic findings in a patient with severe arteriosclerotic heart disease and aortic stenosis. *Am Heart J*. 1962;64:334-346.

314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386

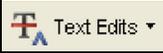
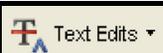
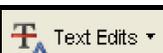
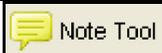
INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

To view, print and annotate your content you will need Adobe Reader version 9 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from <http://get.adobe.com/reader/>. The exact system requirements are given at the Adobe site: <http://www.adobe.com/products/reader/tech-specs.html>.

Note: Please do NOT make direct edits to the PDF using the editing tools as doing so could lead us to overlook your desired changes. Rather, please request corrections by using the tools in the Comment pane to annotate the PDF and call out the changes you are requesting. If you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file.

PDF ANNOTATIONS	
Adobe Reader version 9	Adobe Reader version X and XI
<p>When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on 'Tools', select 'Comment & Markup', then click on 'Show Comment & Markup tool bar' (or 'Show Commenting bar' on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.</p>  <p>(Mac)</p> <p>PDF ANNOTATIONS (Adobe Reader version 9)</p> <p>The default for the Commenting tool bar is set to 'off' in version 9. To change this setting select 'Edit Preferences', then 'Documents' (at left under 'Categories'), then select the option 'Never' for 'PDF/A View Mode'.</p>  <p>(Changing the default setting, Adobe version 9)</p>	<p>To make annotations in the PDF file, open the PDF file using Adobe Reader XI, click on 'Comment'.</p> <p>If this option is not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than XI or the PDF has not been prepared properly.</p>  <p>This opens a task pane and, below that, a list of all Comments in the text. These comments initially show all the changes made by our copyeditor to your file.</p> 

HOW TO...

HOW TO...		
Action	Adobe Reader version 9	Adobe Reader version X and XI
Insert text	<p>Click the 'Text Edits' button  on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.</p>	<p>Click the 'Insert Text' icon  on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_'  in the top right-hand corner.</p>
Replace text	<p>Click the 'Text Edits' button  on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).</p>	<p>Click the 'Replace (Ins)' icon  on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).</p>
Remove text	<p>Click the 'Text Edits' button  on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.</p>	<p>Click the 'Strikethrough (Del)' icon  on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.</p>
Highlight text/ make a comment	<p>Click on the 'Highlight' button  on the Commenting tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.</p>	<p>Click on the 'Highlight Text' icon  on the Comment tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.</p>
Attach a file	<p>Click on the 'Attach a File' button  on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.</p>	<p>Click on the 'Attach File' icon  on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.</p>
Leave a note/ comment	<p>Click on the 'Note Tool' button  on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. <u>Do not use this feature to make text edits.</u></p>	<p>Click on the 'Add Sticky Note' icon  on the Comment tool bar. Click to set the location of the note on the document and simply start typing. <u>Do not use this feature to make text edits.</u></p>

HOW TO...		
Action	Adobe Reader version 9	Adobe Reader version X and XI
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
Undo/delete change	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.

SEND YOUR ANNOTATED PDF FILE BACK TO ELSEVIER

Save the annotations to your file and return as instructed by Elsevier. Before returning, please ensure you have answered any questions raised on the Query Form and that you have inserted all corrections: later inclusion of any subsequent corrections cannot be guaranteed.

FURTHER POINTS

- Any (grey) halftones (photographs, micrographs, etc.) are best viewed on screen, for which they are optimized, and your local printer may not be able to output the greys correctly.
- If the PDF files contain colour images, and if you do have a local colour printer available, then it will be likely that you will not be able to correctly reproduce the colours on it, as local variations can occur.
- If you print the PDF file attached, and notice some 'non-standard' output, please check if the problem is also present on screen. If the correct printer driver for your printer is not installed on your PC, the printed output will be distorted.