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CASE REPORT
Cardiac imaging

Case report on the importance of longitudinal analysis of left ventricular end-systolic volume, rather than ejection fraction, in a heart transplant patient

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Background Sequential determinations of left ventricular (LV) volume constitute a cornerstone in the mechanical performance evaluation of any heart transplant (HTX) patient. A comprehensive analysis of volumetric data offers unique insight into adaptation and pathophysiology.

Case summary With a focus on eight sequential biplane angiocardiographic LV end-systolic volume (ESV) determinations, we evaluate the clinical course of a male patient following HTX (female donor) at the age of 61 years. This former smoker had a history of chronic obstructive pulmonary disease, hypertension, and hypercholesterolaemia refractory to treatment, and presented with multivessel coronary artery disease. The later course was complicated by pulmonary hypertension, an abdominal aortic aneurysm, and secondary chronic kidney disease. After an additional episode of pulmonary embolism, the patient died at the age of 79. At one point, the ESV was > 700% higher than the starting value, and actually by far exceeded the relative change of any other volume-based metric evaluated, including ejection fraction (EF).

Discussion The longitudinal study of LV volumetric data in HTX patients offers a unique window to the pathophysiology of remodelling and sex-specific adaptation processes. The present case documents that proper analysis of serial findings form a rich source of clinically relevant information regarding disease progression. End-systolic volume is the primary indicator, in contrast to the popular metric EF. This finding is supported by population-based studies reported in the literature. We conclude that comprehensive analysis of volumetric data, particularly ESV, contributes to personalized medicine and enhances insight into LV (reverse) remodelling, while also informing about prognosis.

Keywords Heart transplantation • Left ventricular volume • Ejection fraction • End-systolic volume • Ventriculo-arterial coupling • Case report

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Learning points

- Left ventricular end-systolic volume acts as a succinct and clinically relevant biomarker for remodeling during heart transplantation follow-up.
- The combination of end-systolic and end-diastolic volume determines the prevailing working conditions, from which ejection fraction can be derived.
- Ejection fraction may appear to be a misleading indicator of survival after heart transplantation, in contrast to end-systolic volume.

Introduction

Left ventricular (LV) remodelling and its reversal refer to volumetric manifestations of cardiac disease deterioration and response to treatment, respectively. Therefore, cardiac imaging plays a key role during diagnostic procedures and the follow-up trajectory, with end-systolic volume (ESV) and end-diastolic volume (EDV) as main variables.

Traditionally, ejection fraction (EF) is considered a convenient metric to assess ventricular systolic function. However, dimensionless ratios such as EF fail to provide unique information.[1,2] Also, EF is sex-specific,[3] and the same limitations apply to ventriculo-arterial coupling (VAC).[4] This study presents a solution by dissecting the structure of a ratio, and clarifying that the tale about EF is mostly viewed through mathematical lenses yet missing out on physiology. To compensate for the incompleteness of the ratio, a corresponding companion (C) is identified that covers the missing information.[4,5] The necessity to introduce C can be readily understood from a graphical representation as in *Figure 1*, based on the patient discussed. Ejection fraction is an algebraic composite of the variables on the two axes, namely ESV (*y*-axis) and EDV (*x*-axis). Within certain (patho)-physiological constraints, the ESV and EDV can vary (e.g. due to adaptation, rejection, remodelling, or intervention). Each combination of ESV and EDV defines an individual *working point* (e.g. point A or B in *Figure 1*), characterized by the pertinent set of coordinates. This representation clarifies that the slope (ESV/EDV) of the red line through A and B is associated with the prevailing EF = 1 - (ESV/EDV). Clearly, EF alone cannot capture what each combination of ESV and EDV is offering. Similar as in strain analysis, we notice that EF corresponds with *direction*, while *magnitude* [i.e. distance from the origin (labelled S) to point A or B] is defined by EF companion (EFC) = $\sqrt{\{ESV^2+EDV^2\}}$, following the familiar Pythagorean theorem.[4,5]

Values for ESV and EDV demonstrate an unequal impact on EF and EFC. Ejection fraction inversely correlates with ESV: EF = 1–ESV/$(c_1+c_2ESV)\}$, where c_1 and c_2 are population-based constants.[1,6–8] In turn, EFC is strongly associated with EDV.[5] The body surface area indexed (i) ESVi and EDVi generally yield a linear relationship, with stroke volume (SVi) being their difference. The length of the purple arrow in *Figure 1* indicates a particular SVi value for the trajectory of the purple broken line, including point B. This logical representation unifies all relevant details (namely ESVi, EDVi, SVi, EF, and EFCi) within a single graph.[7]

The newer metric VAC also lacks physical units, as it concerns LV end-systolic elastance divided by arterial elastance.[3–5] Facing the limitations inherent to EF and VAC, we concentrate on ESV(i) which key variable also constitutes the core of EF and VAC.[1,2,6,7]

Importantly, ESV(i) is associated with myocardial oxygen consumption (MVO_2), which not only gradually increases with enlarging ESV(i) but also sharply rises for disproportionally small values.[2,7,9]

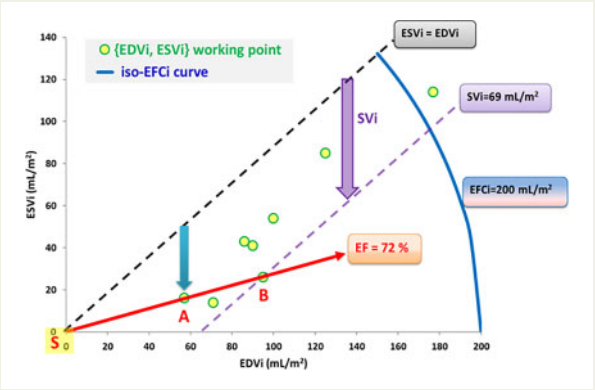
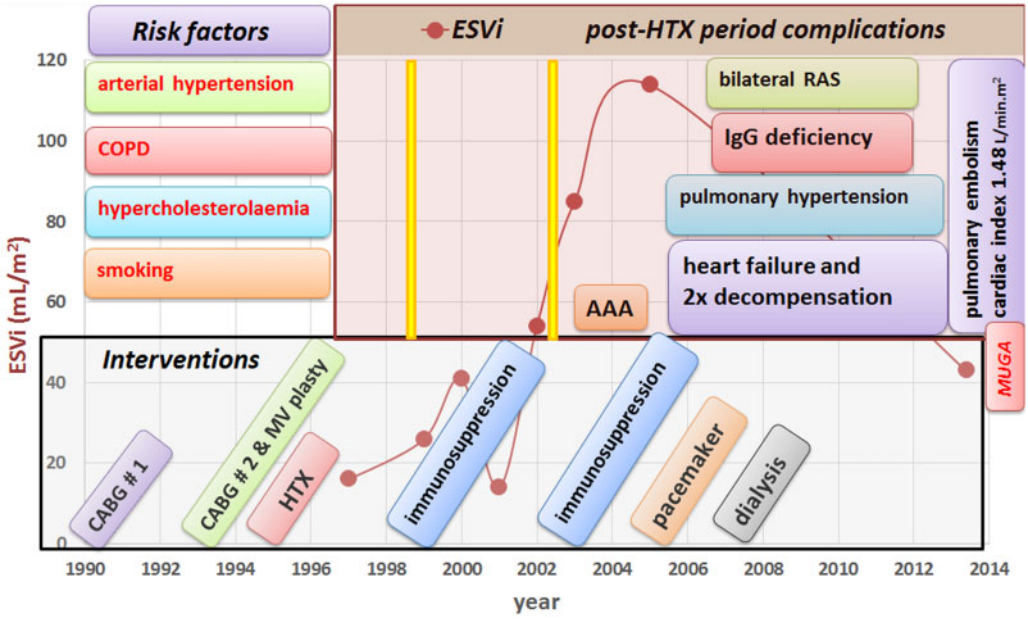


Figure 1 Framework to best visualize the volume regulation throughout the post-transplantation period, showing eight successive working points (i.e. the main volumetric characteristics) of the patient under discussion. This fundamental representation primarily shows end-systolic volume index (ESVi) vs. end-diastolic volume index (EDVi). Most other relevant pump function related metrics are implicit in this graph, e.g. ejection fraction (EF), its companion (EFCi, indexed for body surface area), and stroke volume index (SVi). The broken black line is the identity line, where values for ESVi and EDVi are the same (i.e. SVi = 0, as during an isovolumetric beat). All actual working points are located below this line, as for an ejecting beat ESVi < EDVi. The SVi for any working point {EDVi, ESVi} is found by subtracting the value on the ordinate (i.e. ESVi) from the value on the abscissa (namely EDVi), resulting in (EDVi—ESVi) = SVi (see purple arrow). The broken purple line runs parallel to the identity line, and indicates the trajectory of working points where SVi has a selected fixed value. Working point B is an example, where SVi = 95 - 26 = 69 mL/m^2, corresponding with the length of the purple arrow. The slope of the red line with arrow head equals (ESVi/EDVi) and reflects EF which is defined as 100 × [1 - (ESVi/EDVi)], here expressed as a percentage. Working points A and B happen to yield nearly the same EF (namely 72 and 73%, respectively). Note that A and B refer to different combinations of ESVi and EDVi. In order to distinguish EF(A) from EF(B), we clearly need to consider the distance from each working point to the origin (S) located at {0, 0} of the coordinate system, i.e. compare length of line segments SA and SB. This distance (termed hypotenuse) is denoted as the indexed companion (Ci) to EF. An iso-EFCi curve (in blue) with a fixed hypotenuse value at 200 mL/m^2 is shown as an example (and further explained elsewhere).[4,5] Also, while the EF value for working points A and B is practically the same, it is clear that the corresponding values for SVi greatly differ, as visualized by the unequal length of the blue and purple arrows pointing down from the identity line. In conclusion: neither EF nor SVi alone provides unique information, as each working point is characterized by two variables, namely the pair {EDVi, ESVi} or, alternatively, the combination {EF, EFCi}. Heart rate values for working points shown ranged between 70 and 90 b.p.m.

Energetically, there is a nadir for MVO_2 and an associated optimum range for ESV(i), slightly shifted to the lower region in women.[2,9] Most studies evaluating LV performance after transplantation concentrate on EF, or, more recently on strain analysis. Data interpretation remains of eminent importance, irrespective of imaging modality. As mentioned, ratio-based metrics seem to be inadequate, and ESV(i) may be a promising candidate.

Timeline



Timeline showing various complications (upper right red shaded area) and major interventions (lower grey shaded area), along with the pattern of end-systolic volume index (ESVi) for eight points in time. Active rejection (yellow bars) during the initial years, clearly accompanied by rising ESVi, was treated by immunosuppressives (year 1999/2000, with another episode in 2002). In 2001 the ESVi gradually returned to the baseline level as seen shortly following heart transplant (HTX), but afterwards rose steeply to end 270% above the initial value. AAA, abdominal aortic aneurysm; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IgG, immunoglobulin G; MUGA, multigated acquisition (scan); MV, mitral valve; RAS, renal artery stenosis.

Starting with a bypass operation, this patient with persistent obstructive pulmonary problems, first seen with triple vessel disease and mitral regurgitation (MR), was followed for > 20 years. The *Timeline Figure* graphically summarizes major risk factors, various interventions, and severe complications, along with the biplane angiographically obtained variable (ESVi) which features in this report. The heart transplantation (HTX) at 61 years is the central event and encompasses a subsequent detailed description of (reverse) remodelling, rejections, and deterioration phase. Informed patient consent was obtained. Data are available upon reasonable request.

Case presentation

This Caucasian man, smoker, presented with cardiac complaints at the age of 55 years. He was burdened by additional chronic cardiovascular risk factors, including arterial hypertension, chronic obstructive pulmonary disease, and hypercholesterolaemia (*Timeline Figure*), treated by angiotensin converting enzyme inhibitor, diuretics, statin, and bronchodilators, respectively. Multivessel coronary artery disease and MR were detected during cardiac catheterization. Following repeated coronary artery bypass grafting (CABG), at the age of 61, he underwent orthotopic HTX (female donor) because of ischaemic cardiomyopathy. Active rejection (ISHLT Grade Ia) became manifest within a year, again in 2004, and treated by immunosuppressives (cyclosporine and azathioprine). Besides, he developed an abdominal aortic aneurysm (requiring surgical placement of a 16 mm prosthesis), pulmonary hypertension and bilateral renal artery stenosis (necessitating haemodialysis). In April 2013, pulmonary embolism at the subsegmental branches of the left pulmonary artery was diagnosed. We focus in this report on the imaging aspects during the evaluation of the HTX patient.

Left ventricular volume data inform on two native heart (not shown) and eight successive transplant heart *working points*, i.e. {EDVi, ESVi} combinations. *Figure 1* documents details on pump function, changing over time, while SVi is 61 ± 11 mL/m^2. For two points in time, the EF reveals a value near 72%, yet with two distinct *working points* (A and B), distinguished by their corresponding EFCi values (see line segments SA and SB). Despite the equal EFs, the different ESVi values have consequences for the corresponding MVO_2 estimate, as mentioned before.

The April 2013 angiocardiography (EF = 50%), was followed by a multigated acquisition scan in August 2013, showing a reassuring EF of 64% (just 3 months before his death). However, our report emphasizes cautiousness when interpreting EF in general, and especially in HTX patients. In addition to the interplay (*Figure 1*) among several variables, the *Timeline Figure* illustrates the exclusive time

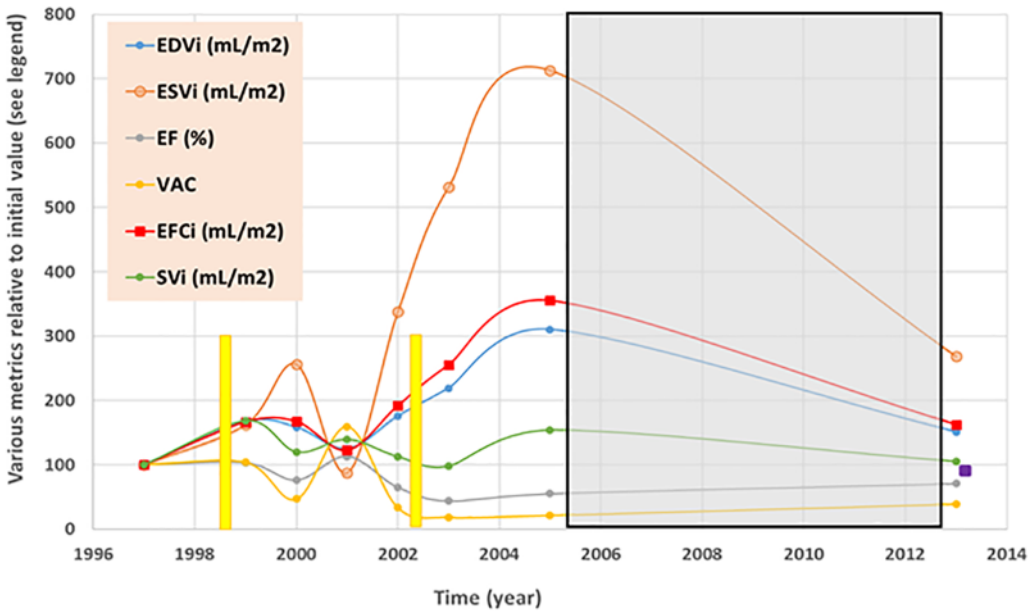


Figure 2 Time pattern of various volume related variables and their derivatives, normalized to starting values. Active rejection phases are indicated by yellow bars. The grey rectangular area marks the later episode where no ventricular volume data were collected. Therefore, the trajectories of the interpolated curves mainly serve the purpose of visually connecting two adjacent datasets, rather than suggesting an observed pattern. At the same time this grey region emphasizes the need to perform volume measurements, nowadays such as those by currently routine echocardiography, even though focus was on serious non-cardiac complications during that period. Note that the last ESVi measurement, taken 6 months before the patient died, was still some 270% above the initial value. The purple symbol to the right refers to ejection fraction according to the multigated acquisition measurement. For ventriculo-arterial coupling (VAC), we calculated a value of 0.55 during the last native heart angiography, as well as for the 7th post-HTX determination. Yet, the associated companion (VACC) differed, yielding 83 and 130 mL/m^2, respectively.

trajectory for ESVi, considered the pivotal variable.[1,2,4] The ESVi-curve clearly reflects deterioration as well as improvement, depending on rejection (marked by the yellow bars), various successful treatments, with the later phase governed by accumulating complications. When normalized to the starting value, the ESVi at one point was > 700% higher (*Figure 2*), and actually by far exceeded the relative change of any other volume-based measure. The last recorded ESVi was 270% above the initial value. The next most pronounced metric in *Figure 2* is the newly introduced EFCi.

Discussion

Our most remarkable finding is that ESVi, rather than EF, plays a prominent role in the clinical evaluation of the patient. Left ventricular volumes are derived from angiography, while also evaluating the coronary tree, and collecting endomyocardial biopsies. Still in 2015 coronary angiography was advocated as the gold-standard method for detecting cardiac allograft vasculopathy (CAV). Since we started following this patient in 1991, various newer (non)invasive imaging modalities were introduced in the routine care of HTX patients, as recently reviewed.[10] Yet, there are currently no clinically validated biomarkers for detecting heart transplant rejection.[10]

Only a few studies explicitly address ESV(i) or permit re-analysis to investigate the impact of this biomarker. One interesting example concerns a radionuclide study (71 patients, 62 male recipients).[11] Survival ranged from 1 (17 patients) to 16 years, with 7 patients >10 years. It was concluded that instability of EF and EDV should prompt further clinical evaluation. Unfortunately, there was no longitudinal evaluation of individual patients, and ESV was not discussed. However, our re-analysis confirms the prominence of ESV as a biomarker (*Figure 3*), as also observed in our case. The figure shows that, compared to 1-year survivors, the relative changes for ESV tend to vary over time. Those surviving >10 years feature steady increases for all variables, VAC and EF excepted. The impact of the popular metric EF (fluctuating within a narrow ±10% band) is less pronounced (yellow area in *Figure 3*), while VAC shows disproportional variations, driven by the dominant ESV component. Concerning rejection, the authors observed a mean frequency of 1.7 ± 1.8 episodes/patient (range 0–7 episodes) for Grade ≥2, with reportedly EF or EDV unrelated to frequency. Another study on 48 HTX patients did address ESVi, where multivariate Cox analysis identified CAV ($P = 0.0039$) and ESVi ($P = 0.008$) as independent predictors of major adverse cardiovascular events.[12]

Most studies on LV volume in HTX patients concentrate on comparing imaging modalities,[10] evaluating groups at various stages,[11] addressing sex-mismatch,[13] or exploring advanced physico-mathematical analysis such as for torsion–displacement loops.[14]

Reinnervation is an important aspect of the post-HTX trajectory. Ricci *et al.*[15] studied nine recipients early (4–10 weeks) after HTX while applying a pacing protocol. By further analysing their data we found that in denervated hearts the EF is uncoupled from ESVi (R =

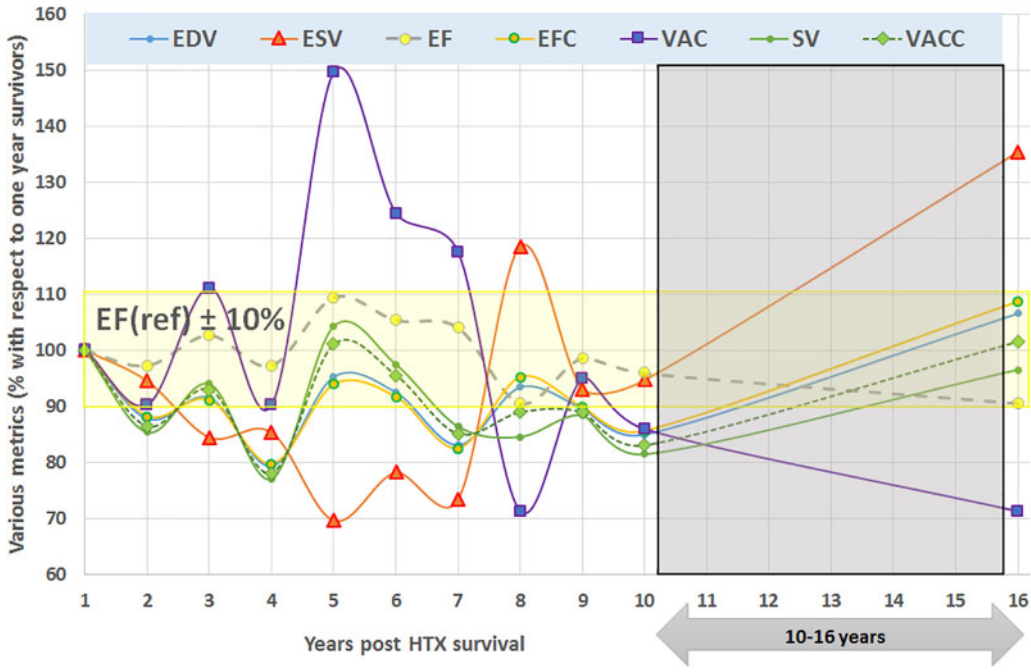


Figure 3 Average literature-based values of major metrics concerning left ventricular function following heart transplant (HTX), all normalized to 100% with reference to the findings for 1-year survivors. Note that this is not a longitudinal study, and that each patient ($N = 71$) appears only once within a group average. Those who survived for more than 10 years constitute a single group; the grey box indicates that individual data are not available and therefore cannot be specified. The popular index ejection fraction (EF) fluctuates within a narrow range (yellow shaded box). Ventriculo-arterial coupling (VAC) displays a rather versatile pattern. For those patients with longest survival in this cohort, it appears that end-systolic volume (ESV) is a strong indicator, similar as in the case which we report here. End-diastolic volume (EDV) parallels EF companion (EFC), as expected. ESV estimated from published EF and EDV data, that were based on radionuclide imaging as obtained by Streeter *et al.*[11]

-0.45), in contrast to R = -0.87 ($P < 0.0001$) for a matched CABG group.[1] Likewise, we calculated that circumferential fibre shortening (a contractility index) correlated with ESVi (R = -0.79) for the controls, but was uncoupled for the HTX group. This means that ESV(i) plays a prominent role in denervated HTX patients. Reportedly, reinnervation starts at 14-month post-HTX, and therefore *Figure 3* may reflect a mixture of reinnervation states.[11]

It remains unclear how to interpret the dimensionless metric EF, because of its dimensionless nature,[4] age-dependence, property as an ordinal metric,[4] consistently higher values found in women compared to their matched male counterparts,[9] and the interference by innervation status.[1,15] In the early denervation state the EF is uncoupled,[1] even more so than with chronic beta-blockade.[1,6] The same limitations apply to VAC (see *Figure 2*). This inherent ambiguity implies that EF or VAC cannot be directly associated with 'function' in terms of physiology. In contrast, ESV(i) is a linear scale variable and predictive of MVO_2, showing a swoosh shaped pattern with a nadir in the ESVi range from 25 to 40 mL/m^2.[2,7,9] Therefore, we propose focusing on ESV(i) in the volume domain (*Figure 1*), rather than relying on disheartening ratios such as EF or VAC.

Conclusions

A comprehensive analysis of imaging data documents that ESV(i), rather than EF or VAC, is the primary clinically relevant indicator in this HTX patient, who was characterized by a complex disease history, further complicated during the postoperative course. Our main findings concerning LV volume-based variables are supported by a re-analysis of similar imaging studies reported in the literature. The connection between EF and ESVi is lost after denervation, meaning that EF is not a preferred metric in HTX patients during their early phase. Besides, the EF is not a metric that permits a unique interpretation. Thus, longitudinal imaging studies regarding individual HTX patients should be encouraged and evaluated with a prominent place for ESV(i), rather than on the basis of dimensionless ratios.

Lead author biography

Dr Kerkhof obtained a PhD at the Paediatrics department, Leiden University Medical School. As a Fogarty NIH fellow with a passion for

cardiology research, he first joined Harvard Medical School and then the University of Pennsylvania. At the World Congress of Cardiology in Moscow, he was a Young Investigator Award finalist and presented a paper on the importance of end-systolic volume for the evaluation of cardiac pump function. Together with Prof. Virginia Miller, he co-edited a book entitled 'Sex-Specific Analysis of Cardiovascular Function'. His current interests focus on a more comprehensive description of ratio-based metrics in cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that, in line with COPE guidance, written consent for submission and publication of this case report has been obtained from an authorized relative of the patient.

Conflict of interest: None declared.

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