SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Arterial Tonometry

Arterial tonometry was performed immediately before or after CMR using a SphygmoCor Px device (AtCor Medical, Inc., Lisle, IL), equipped with a high-fidelity Millar applanation tonometer (Millar Instruments, Houston, Tx). Brachial blood pressure was obtained using a validated oscillometric device (Omron 705CP-II; HEM-759P-E2). Radial waveforms were recorded and calibrated with brachial systolic and diastolic pressure. An aortic pressure waveform was obtained via the generalized transfer function of the Sphygmocor device. Carotid-femoral pulse wave velocity (CF-PWV) was obtained via sequential carotid and femoral tonometry using the QRS complex as a fiducial point to assess the pulse transit time between these 2 locations; CF-PWV was computed as distance/time (m/s).

Measurements of LV mass

CMR scans were performed using a 1.5 Tesla (T) whole body MRI scanner (Avanto or Espree, Siemens, Malvern, Pennsylvania) equipped with a phase-array cardiac coil. LV volumes and ejection fraction (EF) were determined using balanced steady-state free-precession (SSFP) cine imaging. Typical parameters were as follows: TR=30.6 ms; TE=1.3 ms; Phases=30; Slice thickness=8 mm; Matrix size=192x192; Parallel image (IPAT) factor=2 to 3. LV short-axis stack cine images were manually traced at end-diastole and end-systole using CMR42 software (Circle CVI, Calgary, AB, Canada). LV

mass (LVM) was computed as the difference between epicardial and endocardial volumes, multiplied by myocardial density.

Flow measurements

To compute the input impedance of the systemic arterial tree (aortic input impedance) and assess wave reflection magnitude, knowledge of the time-resolved proximal aortic inflow (which equals LV outflow) is required. Proximal aortic flow was measured using through plane velocity-encoded phase-contrast imaging with a plane prescribed perpendicular to the long axis of the aorta at the level of the right pulmonary artery; (typical parameters were as follows: TR~10 msec; TE=3.2 ms; Flip angle=30; FOV=340x340; matrix size=256-256; Slice thickness=8 mm; gating=retrospective; VENC=at least, 130 cm/sec, prescribed *ad hoc* to avoid aliasing). Aortic through-plane phase-contrast images were processed with Segment software (Segment v1.8R0936; Medviso, Lund, Sweden). (1) When significant aliasing impeded a reliable assessment of the proximal aortic systolic flow profile, we used the systolic LV outflow profile obtained from a 2-D encoded, in-plane phase contrast acquisition in the 3-chamber LV long axis plane. In all cases, diastolic outflow was set to zero and the time-integral of the systolic flow curve was calibrated to the stroke volume measured via LV cine imaging.

Arterial Load

Arterial load was quantified using custom-designed software programmed in MATLAB (MathWorks, Natick, MA). Briefly, after alignment of central pressure and flow waveforms proximal aortic characteristic impedance (Z_C), which describes the

relationship between pulsatile pressure and flow in the absence of wave reflections, was computed in the frequency domain, as the mean value of input impedance moduli at higher harmonics (**Figure 1**). Linear wave separation analysis was performed to decompose the pressure waveform into its forward (Pf) and backward (Pb) components. This wave separation is based purely on the pulsatile components of pressure and flow, and thus does not incorporate mean load (total peripheral resistance). Pf and Pb thus fluctuate around zero. The reflected wave transit time was computed as the difference in the time at which the forward and backward wave start adding to pressure, as previously described (**Figure 1**).

Quantification of Aortic PWV

For sensitivity analyses, we performed an additional measurement of aortic PWV using phase-contrast MRI, using in-plane velocity encoding from head to foot in the aortic "candy cane" view. We defined regions of interest along the aortic lumen, from which velocity curves were extracted. A velocity-time curve was obtained from each of several ROIs along the aortic centerline. Centerline distance was measured from the magnitude images. A spatiotemporal flow profile was generated, and PWV was computed as the slope of distance over time, obtained from linear regression. This method effectively computes PWV as distance / Δ time using multiple flow curves (rather than just two) along the aortic lumen.

Extracellular volume measurements

We used a modified Look-Locker inversion recovery (MOLLI) (12) sequence to assess T1 times prior to and following the intravenous administration of gadolinium contrast (MultiHance, 0.15 mmol/kg of body weight or equivalent) in a mid-ventricular short-axis slice. MOLLI sequences were not available in one of the recruiting centers. ECV was measured in 31 subjects enrolled across the other sites. Scan parameters for MOLLI protocol included: field of view (FOV)~340 mm; matrix size=144x192; slice thickness=6 mm; repetition time=24.9 ms; echo time=1.18 ms; flip angle=30. Myocardial T1 measurements were performed before and at several time points at least 10 minutes after-gadolinium administration. All available blood and myocardial T1 measurements at >10 minutes after injection (~10, 15 and 20-30 min) were used to compute the myocardium-blood partition coefficient (lambda) (5, 14, 18) as the slope of the blood 1/T1 over the myocardial 1/T1 change, via linear regression. Lambda was used to compute the LV ECV fraction (ECVF) as follows: ECVF=lambda*(1-hematocrit). LV extracellular mass was computed as LV mass multiplied by ECVF. LV cellular mass was computed as LV mass multiplied by (1-ECVF).

Supplemental Results

Table S2 shows a comparison of subject who underwent a follow-up MRI (n=30) vs. those who did not (n=8). Subjects who could not undergo a follow-up MRI tended to be older and demonstrated a lower prevalence of thiazide use at baseline.

Table S3 shows comparisons of parameters of arterial load between subjects stratified according to the median value of extracellular mass at baseline (pre-AVR). Some of these comparisons are shown in **Figure 3**.

Figure S2 shows the mean change in various domains of the KCCQ scores between the pre-AVR and post-AVR assessments. A positive change (i.e., higher scores post-AVR) indicate an improvement. **Table S4** shows the correlation coefficients (and 95%Cis) between reflection magnitude at baseline (pre-AVR) and the improvement in various domains in the KCCQ scores after AVR (post-AVR minus pre-AVR value); these data are demonstrated in the right panel of **Figure 4**.

Sensitivity analyses

There were 3 eligibility waivers during the study. Two subjects were felt to have a mildly reduced LV ejection fraction (40-50%) based on clinical imaging (one prior to enrollment and one after enrollment). However, in both cases, the LVEF obtained from core lab MRI quantification was >50%. A third case underwent a non-gadolinium enhanced cardiac MRI with similar LV and flow acquisitions within 1 week prior to enrollment in the study. To avoid excessive burden on the participant, a repeat MRI with gadolinium administration was waived. Following a recommendation from our data safety monitoring board, we conducted an analysis excluding these subjects. In these sensitivity analyses, observed trends and estimates were very similar to the overall results (not shown).

Table S1. Glossary of key indices of arterial load and ventricular arterial interaction.

Parameter	Definition and interpretation
Aortic input impedance (Zin)	Spectrum of frequencies obtained when aortic pressure and flow waveforms are decomposed into their harmonics and pressure harmonics are divided by corresponding flow harmonics. Impedance modulus is calculated as pressure modulus/flow modulus and impedance phase is computed as pressure phase minus flow phase. Input impedance is therefore not a single number. Various arterial parameters can be obtained from the impedance spectrum. An example of an input impedance spectrum (modulus and phase) is shown in Figure 1 of the main manuscript.
Total peripheral resistance	Ratio of mean pressure to mean flow. Represents the steady (non-pulsatile) vascular load. Determined by arteriolar diameter and tone and rarefaction.
Aortic root characteristic impedance (Zc)	Ratio of pulsatile pressure to pulsatile flow in the absence of wave reflection. It is the pulsatile impedance to LV ejection exerted by the aortic root and physically represents the combined effects of the inertia of the blood to systolic acceleration and the ability of the aorta to locally store the blood. It governs the early systolic pulsatile pressure-flow relation (before arrival of wave reflections to the LV), and thus, is a key determinant of early systolic pulsatile arterial load. It is determined by aortic root size (smaller roots provide a greater Zc) and to a lesser degree, aortic root wall stiffness (a stiffer root wall provides a greater Zc).
Forward pressure wave (Pf)	Composite wave, travelling from the heart to the periphery, that includes: (1) The primary wave generated by the heart; (2) Peripheral wave reflections that are "rectified" (i.e., re-reflected) at the heart or the aortic valve. It is a parameter of cross-talk between the LV, the aortic root and peripheral reflection sites.
Backward pressure wave (Pb)	Composite wave, travelling from the periphery towards the heart, influenced by: (1) The magnitude of the forward wave; (2) Reflection coefficients at distributed sites along the arterial tree; (3) Pulse wave velocity to and from reflection sites. These factors interact in complex ways to form a discrete net reflected wave measured at the aortic root. It is a parameter of ventricular-arterial cross-talk.
Reflection magnitude	Ratio of backward/forward wave amplitude. It does not account for the timing of the backward wave. Similarly, it does not characterize the contribution of the reflected wave to systole vs. diastole. It is determined by distributes sites of impedance mismatch along the arterial tree (middle-sized muscular arterial segments, aortic tapering, (focal) wall stiffening and/or narrowing in conduit arteries, microvasculature).

Valvuloarterial impedance	Ratio of (mean transvalvular gradient + systolic blood pressure) to stroke volume index. It represents the cost in mmHg for each systemic ml of blood pumped by the LV during systole. It is a useful index of LV load, but it does not adequately capture the contribution of pulsatile arterial load and the systolic loading sequence. Therefore, time-resolved pressure-flow analyses provide information above and beyond the valvuloarterial impedance.
Total arterial compliance	Theoretical compliance of the entire arterial tree. Derived from Windkessel modeling, which does not explicitly account for wave propagation and reflection. In the systemic circulation is it provided mostly by the ascending aorta and arch and large proximal arteries and to a lesser extent, muscular arteries and smaller vessels.
Pulse wave velocity (PWV)	Propagation velocity of the pulse wave travelling through the arterial wall. PWV is related to the elastic modulus of the wall material and the wall thickness/lumen ratio. Currently considered the "gold standard" non-invasive metric of arterial stiffness and usually assessed as the ratio of the estimated distance between the carotid and femoral artery, and the measured time delay between a hemodynamic signal (such as a pressure or flow waveform) measured at these sites.

For a more detailed explanation of these parameters, we refer the reader to the following review paper**:** Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: Part 2: Arterial pressure-flow and pressure-volume relations in humans. *Hypertension*. 2010;56:563-570.

Table S2. Comparison on Subjects who did and did not undergo a CMR study after AVR.

	Underwent a Follow-up CMR (n=30)	Did not undergo Follow-up CMR (n=8)	*P* value
Age	70.8±9.3	77.1±8.1	0.09
Male sex	21 (70.00%)	5 (62.50%)	0.69
Race/Ethnicity			1.00
Caucasian	28 (93.33%)	8 (100.00%)	
African American	2 (6.67%)	0 (0.00%)	
BMI, kg/m^2	30.9±6	28.1±5.7	0.24
Serum creatinine	0.911±0.21	0.876±0.209	0.68
Aortic valve area (cm^2)	0.751±0.139	0.675±0.157	0.19
Aortic valve area index (cm^2/m^2)	0.372±0.082	0.34±0.072	0.32
Mean transvalvular gradient (mmHg)	47.1±13.1	52.9±18.7	0.32
Peak transvalvular gradient (mmHg)	88.3±31.5	74.1±21.7	0.15
Valvulo-arterial impedance, mmHg•ml^{-1}•m^2	4.17±1.1	4.48±1.05	0.48
Systolic Blood Pressure mmHg	129 (126,153)	139 (128,160)	0.51
Diastolic Blood Pressure, mmHg	72.9±9.6	73.8±11.2	0.83
Mean arterial Pressure, mmHg	99.7±13.4	94.9±12.6	0.37
Pulse pressure, mmHg	70.6±26.4	63±6.8	0.43
Heart rate, bpm	62.5 (57,73)	65 (54.5,73.5)	0.97
Angina	1 (3.33%)	0 (0.00%)	1.00
Dyspnea	22 (73.33%)	4 (50.00%)	0.23
Diabetes Mellitus	9 (30.00%)	3 (37.50%)	0.69
Hypertension	27 (90.00%)	6 (75.00%)	0.28
NYHA Class			0.36
I	7 (23.33%)	3 (37.50%)	
II	14 (46.67%)	5 (62.50%)	
III/IV	7 (23.33%)	0 (0.00%)	
Medication Use			
Aspirin	23 (76.67%)	8 (100.00%)	0.31
ACE Inhibitors or ARBs	17 (56.67%)	7 (87.50%)	0.22
Beta Blockers	18 (60.00%)	4 (50.00%)	0.70
Calcium Channel Blockers	7 (23.33%)	1 (12.50%)	0.66
Thiazide diuretics	12 (40.00%)	0 (0.00%)	0.04
Loop diuretics	6 (20.00%)	0 (0.00%)	0.31
Hydralazine use	0 (0.00%)	1 (12.50%)	0.21
Long Acting Nitrate use	0 (0.00%)	1 (12.50%)	0.21
Insulin Use	3 (10.00%)	1 (12.50%)	1.00

Numbers represent mean±SD for normally-distributed variables, median (IQR) for non-normally distributed variables, or counts (%). *P* values were obtained using the unpaired t test for normally distributed variables, the Kruskall-Wallis test for non-normally distributed variables, and the chi-square or Fisher exact test for proportions, as appropriate.

Table S3. Comparisons of Parameters of Arterial Load between subjects with Higher vs Lower Extracellular Mass at baseline (pre-AVR), stratified according to the median value.

	Extracellular Mass<35.6 g Mean (95%CI)	Extracellular Mass (g) ≥35.6 g Mean (95%CI)	*P* value
Reflection Magnitude	0.54 (0.47 to 0.60)	0.68 (0.61 to 0.74)	0.006
Aortic Zc, dynes·s/cm^5	96.9 (73.3 to 120.5)	56.3 (33.5 to 79.2)	0.025
Reflected Wave Transit time, s	0.045 (0.035 to 0.054)	0.039 (0.03 to 0.048)	0.42
Carotid-femoral PWV, m/s	8.8 (6.6 to 10.9)	9.9 (7.9 to 12)	0.437
Total peripheral resistance, dynes·s/cm^5	1387 (1221 to 1553)	1175 (1014 to 1335)	0.083
Valvuloarterial impedance, mmHg·ml^{-1}·m^2	4.21 (3.73 to 4.68)	3.55 (3.08 to 4.03)	0.066
Systolic blood pressure (mmHg)	142 (135 to 150)	134 (126 to 142)	0.1358
Diastolic blood pressure (mmHg)	74.8 (70.6 to 79)	72.7 (68.5 to 76.9)	0.5001
Pulse pressure (mmHg)	67.5 (60.8 to 74.3)	61.1 (54.4 to 67.9)	0.1974

Table S4. Correlation Between Reflection Magnitude at Baseline (pre-AVR) and the improvement in KCCQ after AVR (change compared to pre-AVR value).

	Correlation Coefficient	95% CI	*P* value
Physical Limitation Score change	-0.52	-0.85 to -0.19	0.003
Symptom Stability Score change	0.12	-0.25 to 0.49	0.52
Symptom Frequency Score change	-0.32	-0.67 to 0.04	0.076
Symptom burden Score change	-0.53	-0.85 to -0.21	0.002
Total Symptom Score change	-0.46	-0.79 to -0.12	0.009
Self-Efficacy Score change	0.17	-0.2 to 0.54	0.356
Quality of Life Score change	-0.38	-0.72 to -0.03	0.034
Social Limitation Score change	-0.43	-0.78 to -0.08	0.018
Overall Summary Score change	-0.51	-0.83 to -0.19	0.003
Clinical summary Score change	-0.50	-0.82 to -0.17	0.004

Figure S1. Study subject flow and procedures.

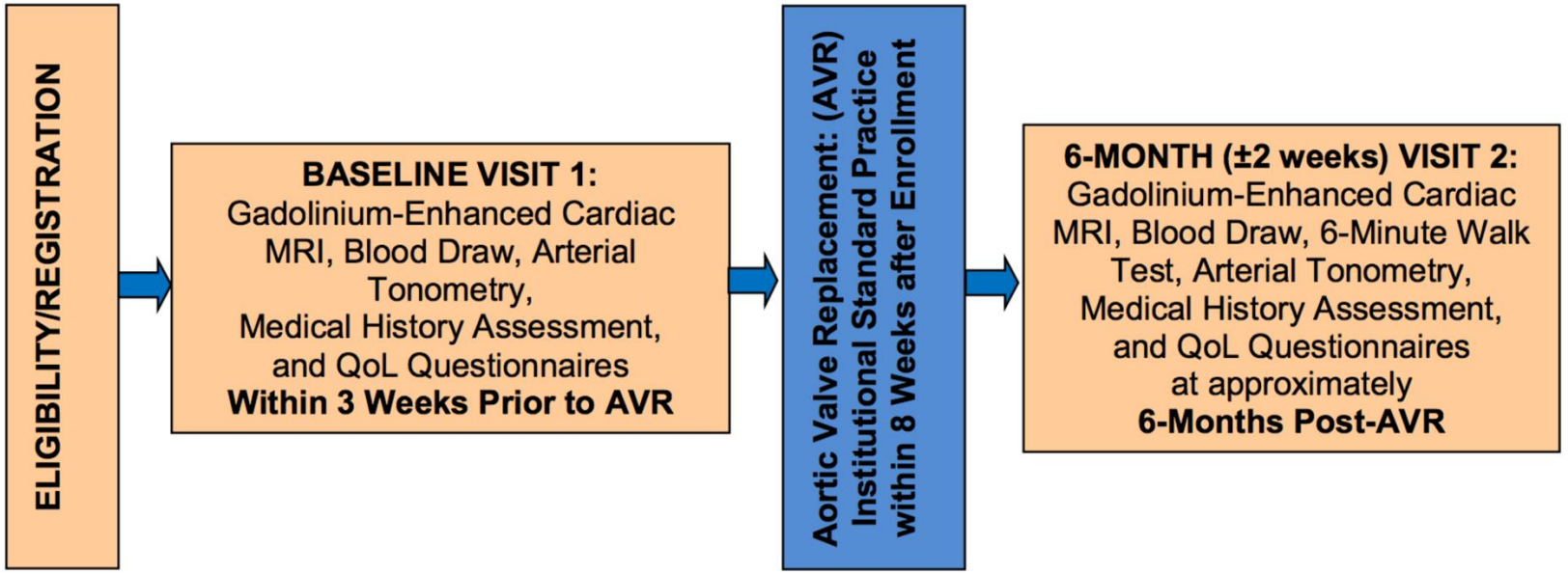
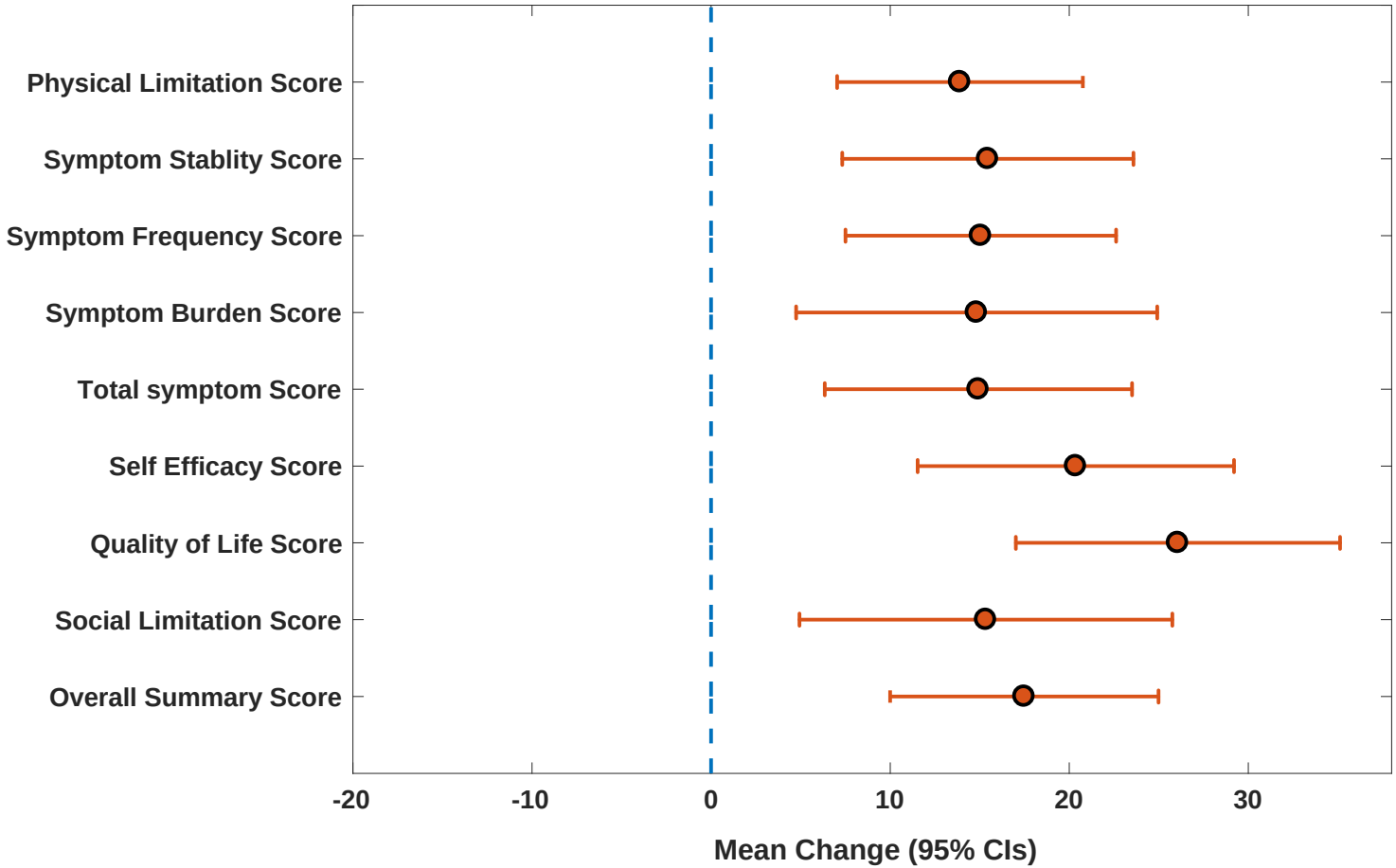


Figure S2. Mean change in KCCQ scores between the pre-AVR and post-AVR assessments. A positive change (i.e., higher scores post-AVR) indicate an improvement.



KCCQ=Kansas City Cardiomyopathy Questionnaire. AVR=aortic valve replacement.

Supplemental Reference:

1. Heiberg E, Sjogren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of Segment--freely available software for cardiovascular image analysis. *BMC Med Imaging.* 2010;10:1.