The thick left ventricular wall of the giraffe heart normalises wall tension, but limits stroke volume and cardiac output

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Abstract

Giraffes – the tallest extant animals on Earth – are renowned for their high central arterial blood pressure, which is necessary to secure brain perfusion. The pressure which may exceed 300 mmHg has historically been attributed to an exceptionally large heart. Recently, this has been refuted by several studies demonstrating that the mass of giraffe heart is similar to that of other mammals when expressed relative to body mass. It remains enigmatic, however, how the normal-sized giraffe heart generates such massive arterial pressures.

We hypothesized that giraffe hearts have a small intraventricular cavity and a relatively thick ventricular wall, allowing for generation of high arterial pressures at normal left ventricular wall tension. In nine anaesthetized giraffes (495±38 kg), we determined in vivo ventricular dimensions using echocardiography along with intraventricular and aortic pressures to calculate left ventricular wall stress. Cardiac output was also determined by inert gas rebreathing to provide an additional and independent estimate of stroke volume. Echocardiography and inert gas-rebreathing yielded similar cardiac outputs of 16.1±2.5 and 16.4±1.4 l min⁻¹, respectively. End-diastolic and end-systolic volumes were 521±61 ml and 228±42 ml, yielding an ejection fraction of 56±4%, and a stroke volume of 0.59 ml kg⁻¹. Left ventricular circumferential wall stress was 7.83±1.76 kPa. We conclude that, relative to body mass, a small left ventricular cavity and a low stroke volume characterizes the giraffe heart. The adaptations result in typical mammalian left ventricular wall tensions, but results in lowered cardiac output.

Key words: giraffe, heart, left ventricle, end diastolic volume, cardiac output
Introduction

Giraffes – the tallest extant animals on Earth – are renowned for their high mean arterial blood pressure (MAP) at heart level (>300 mm Hg in systole) that provides for typical mammalian cerebral perfusion pressures even when the brain is positioned several meters above the heart (Goetz and Budtz-Olsen, 1955; Van Citters et al., 1968; Van Citters et al., 1969; Mitchell et al., 2006; Brøndum et al., 2009). In a series of legendary studies on the influences of posture and gravity on the cardiovascular systems of giraffes, Goetz and colleagues reported that the high MAP is achieved by virtue of an exceptionally large heart (Goetz, 1955). This intuitively appealing notion became widely accepted and even inspired the development of the so-called “giraffe-language” as a euphemism for compassionate communication (Rosenberg, 1999). However, several recent and independent investigations, based on much larger sample sizes than the original studies by Goetz, now reveal that giraffes are merely endowed with the same relative cardiac mass as all other mammals, i.e. 0.5-0.6% of body mass (Brøndum et al., 2009; Mitchell and Skinner, 2009; Østergaard et al., 2013; Perez, 2008). Incidentally, Edwards Crisp (1864a; 1864b) had already reported normal mammalian heart size in giraffes by the middle of the nineteenth century, and Goetz’s original report therefore appear erroneous (Mitchell and Skinner, 2009).

While the normal size of the giraffe heart now appears well-established, it remains enigmatic how the high MAP is generated. As noted by Seymour and Blaylock (2000), ventricular wall stress seems to be very similar amongst mammals. When the left ventricle is simplified to assume the shape of a thick-walled cylinder, the principle of Laplace states that the mechanical stress exerted on the myocardial wall is proportional to left ventricular pressure (LVP) and its midwall radius (r), whilst it is inversely proportional to wall thickness (WT):

$$\text{wall stress} = \frac{LVP \times r}{WT}$$

Thus, an attractive possibility is that the giraffe heart has normalized wall-stress in response to the high intraventricular blood pressure by having a lower left ventricular radius and a thicker ventricular wall (Mitchell and Skinner, 2009). This can be achieved by a typical mammalian heart mass relative to body mass, but must entail a lower stroke volume (SV) per unit of cardiac mass than in similar-sized mammals (see Figure 1, which also shows the gross morphology of the giraffe heart). Consequently, if heart rate of the giraffes is similar to that of similar-sized mammals, then cardiac output per mass unit must be substantially lower. To investigate the hypothesis that giraffes have a volumetrically small heart with a low intraventricular radius, we determined left ventricular systolic and diastolic dimensions, including wall thicknesses in young anaesthetised giraffes by echocardiography. We obtained simultaneous intraventricular blood pressures to
calculate ventricular wall stresses. We also performed additional and independent measurements of cardiac output using inert gas rebreathing technique allowing SV to be assessed by two independent and principally different methods.

**Materials and Methods**

These studies were part of the second expedition by The Danish Cardiovascular Giraffe Research Programme (DaGIR) in October-November (2010) to Hammanskraal (Gauteng Province) in South Africa.

**Experimental animals**

Experiments were performed on eight juvenile male giraffes (*Giraffa camelopardalis*, Linnaeus, 1758) with an estimated age of 14 to 52 months, a body mass ranging from 330 to 654 kg (495±38 kg; mean ± s.e.m.), and a standing height of 3.4 to 3.9m. All animals were bred for trophy hunting in Namibia and were maintained in a quarantine facility in Hammanskraal for up to two months prior to the experiments. The experimental protocol was approved by the national Danish Animal Experiments Inspectorate (Danish Ministry of Justice), the Animal Ethics Screening Committee at the University of Witwatersrand (Johannesburg) and the Animal Use and Care Committee (University of Pretoria). Local ethical committee members oversaw the experiments and permission to euthanize the animals was granted by the Gauteng Province of South Africa.

**Animal handling and anaesthesia**

All studies were performed on anaesthetized giraffes using an experimental protocol and a set-up as described previously by Brøndum et al. (2009); following overnight fast and 2h without water, the giraffes were sedated with medetomidine (6µg kg\(^{-1}\), i.m.), and guided to a chute where they were blindfolded. Anesthesia was induced by remote injection of etorphine (9 µg kg\(^{-1}\), i.m.) and ketamine (0.9 mg kg\(^{-1}\), i.m.), which rendered the giraffes recumbent within minutes. As soon as the animals were recumbent, a cuffed endotracheal tube (ID 20 mm) was inserted to allow ancillary ventilation with oxygen using a demand valve (Hudson RCI, USA). After supplementary dose of ketamine (0.2 mg kg\(^{-1}\), i.v.), the giraffes were placed in right lateral recumbency on a custom made movable platform. Animals were allowed to breathe spontaneously, but were mechanically ventilated if necessary to maintain normal end-tidal CO\(_2\) and arterial blood gases. Anesthesia was maintained by continuous infusion into the saphenous vein of α-chloralose (KVL Pharmacy, Frederiksberg, Denmark; 30 mg kg\(^{-1}\) h\(^{-1}\) gradually decreasing guided by clinical signs) in the saphenous vein. Following systemic administration of heparin (150 units kg\(^{-1}\); 25.000 IE/ml, B Braun, Melsungen, Germany) and local infiltration by lidocaine (2%, SAD, Copenhagen, Denmark),
vascular sheaths were placed in the carotid artery and jugular vein at the base of the neck. Using limb straps to avoid pressure on the thoracic and abdominal regions, the platform was used to hoist the giraffe to an upright position. To minimize the influence of the induction agents on the cardiovascular system, the effect of the etorphine was reversed with naltrexone, and measurements were obtained after the effects of medetomidine and ketamine were expected to have subsided (more than 90 min after administration; Brøndum et al., 2009).

The cardiovascular measurements completed in the present study would be virtually impossible to achieve in conscious animals where the necessary restraint and handling stress would be ethically unacceptable and cause considerable disturbances of haemodynamic variables. The anaesthetics themselves, on the other hand, also influence the cardiovascular system; however as mentioned above the effects of ethorphine and medetomidine must be considered very small and α-chloralose is regarded to have smaller effects on circulation than most other anaesthetics and furthermore allowed for a dynamic regulation of anaesthesia depth (Covert et al., 1992).

**Measurements of cardiac output**

Cardiac output (Q) was determined in 9 spontaneously breathing giraffes using the inert gas rebreathing technique (Innocor Inert Gas Rebreather, Innovision, Glamsbjerg, Denmark; Clemensen et al., 1994). Rebreathing was performed over a minimum of 5 breaths to ensure complete mixing of the gases with the air in the respiratory system. The experimental site was located at approximately 1200 meters above sea level, and therefore we corrected for the actual barometric pressure. The rebreathing technique provides a reliable measure of effective pulmonary blood flow (Gabrielsen et al., 2002), but could underestimate systemic cardiac output in the presence of pulmonary shunts. During all rebreathing procedures, the arterial oxygen saturation exceeded 97% or above, indicating no or minimal pulmonary shunting.

**Hemodynamic parameters**

A tip transducer catheter (5 French Micro-Tip SPC 350, range -50 to 400 mmHg; Millar Instruments, Houston, TX, USA) was advanced through the carotid artery into the ascending aorta for continuous recording of MAP using a Biopack Systems data acquisition software (AcqKnowledge 3.7.2) at 100 Hz. The second catheter was advanced into the left ventricle for measurements of left ventricular pressure (LVP).

**Echocardiography**

A conventional transesophageal echocardiography probe (6T-RS TEE transducer, GE Healthcare, UK) covered with a plastic sheath was inserted into the left jugular vein through the cut-down in the neck and secured with a purse string. A portable echocardiography apparatus was used for
data acquisition and storage (Vivid Q, GE healthcare, UK). For long-axis imaging including the aortic root- and valve, the mitral valve, the septum and the lateral wall of the left ventricle (similar to a five chamber view in humans), the probe was advanced towards the right atrium just above the tricuspid valve. We measured diastolic- and systolic long-axis lengths defined as the distance from the hinge point of the anterior mitral valve leaflet to the ventricular apex. In some animals this length exceeded the depth range of the probe, so the apex could not be defined. In these instances the position of the apex was defined as the intersection of extrapolated lines from the septal and lateral wall endocardium. Subsequently, a partial left thoracotomy exposed the rib cage and through appropriate intercostal spaces equatorial short-axis- and long axis cine-recordings were completed with a conventional transthoracic echocardiographic probe (3S TTE transducer, GE Healthcare, UK). We measured the diastolic- and systolic short-axis endocardial- and epicardial diameters from the septum to the lateral wall, defining the right ventricular endocardial border as the septal “epicardium”. Diastolic and systolic wall thicknesses were measured in the septum and in the free wall.

All giraffes were killed with intravenous pentobarbital (20%, KVL Pharmacy) and weighed. The heart was excised and weighed.

Calculated hemodynamic parameters

Long-axis- and short-axis shortening, and wall thickening were calculated as the absolute difference between the diastolic- and systolic values divided by the diastolic value of the parameter. For calculation of chamber volumes, the left ventricle was assumed to have the shape of a prolate hemi-ellipsoid with volume:

\[ V = \frac{2}{3} \pi \left( \frac{D}{2} \right)^2 L, \]

where \( D \) is the short-axis or the diameter \((D/2)\) thus equals the internal radius of the left ventricle) and \( L \) is the long-axis. Accordingly, end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), and ejection fraction (EF) was calculated using the diastolic- and systolic long-axis- and endocardial short-axis measurements described above. Cardiac output (Q), in absolute values and expressed relative to body mass, was calculated using the mean heart rate over the time span of the echocardiographic measurements. Taking the ellipsoid shape of the left ventricle into account, the systolic circumferential- and meridional wall stresses (CWS and MWS, respectively) were calculated in kPa as:

\[ CWS = 133.322 \times \frac{\text{mmHg}}{\text{kPa}} \times \frac{\Delta P_{sys} \times D/2}{WT} \times \left( 1 - \frac{WT}{D} - \frac{D/2}{L^2} \right). \]
\[ MWS = 133.322 \frac{kPa}{mmHg} \times \frac{AP_{sys} \times D/2}{2 \times WT(1 + WT/D)} \]

where \( AP_{sys} \) is the mean systolic arterial pressure (mmHg) over the time span of the echocardiographic measurements, \( D \) is the systolic endocardial short-axis diameter, \( L \) is the long-axis of the ventricle, and \( WT \) is the systolic wall thickness (Grossman et al., 1975; Mirsky, 1969).

**Net external work by the left ventricle**

Simultaneous measurements of left ventricular pressures and pulmonary flow by the inert gas rebreathing technique were performed on six animals, and allowed for net external work of the heart (\( W \)) to be calculated as

\[ W = \Delta LPV \times Q, \]

where \( \Delta LPV \) the change in left ventricular pressure (approximated as the systolic minus the diastolic pressure).

**Systemic vascular resistance**

Systemic vascular resistance (SVR) was calculated as

\[ SVR = \frac{MAP - P_{RA}}{Q} \]

where \( MAP \) is the mean arterial blood pressure, \( P_{RA} \) the right atrial pressure and \( Q \) is cardiac output.

**Diffusion tensor imaging (DTI)**

To visualize the three-dimensional architecture of the left ventricular myocardium in terms of cardiomyocyte pathways we performed Diffusion Tensor Imaging with MRI, on one giraffe heart with a Philips 1.5 T Achieva system. The heart was placed in the magnet oriented with the long axis parallel to the axis of the main magnetic field, and a surface receiver-coil was used for data reception. A diffusion tensor imaging sequence was applied using 32 different diffusion-weighted directions. The principal direction of the diffusion tensor was calculated in each voxel. A number of voxels of interest were selected from this three-dimensional matrix, and based upon the characteristics of the primary eigenvectors, the algorithm then calculated any possible “track”, or pathway, which passes through the chosen voxels of interest (Smerup et al., 2009).
**Statistical analysis**

Measurements were analysed with paired or unpaired t-test as appropriate. A statistical significance level of $p<0.05$ was used, and data are expressed as mean ± s.e.m.

**Results**

**Ventricular dimensions and pressures in vivo**

The echocardiography provided adequate visualization of the beating giraffe heart *in vivo* (see supplementary material movie 1 and Figure 2) and hence allowed for determination of cardiac dimensions during the entirety of the cardiac cycle. As shown by the example in Figure 3, we obtained simultaneous measurements of aortic pressures as well as the pressures within each ventricle. During the echocardiography, MAP was $224±7$ mmHg, and the systolic pressures within the left and right ventricle were $234±7$ and $45±3$ mmHg, respectively with a heart rate of $56±5$ min$^{-1}$.

The diastolic- and systolic long-axis lengths were $18.2±0.3$ and $15.5±0.3$ cm, respectively ($p<0.001$), resulting in long-axis fractional shortening of $14.9±0.3\%$. The corresponding endocardial short-axis values were $7.3±0.5$ and $5.2±0.4$ cm ($p<0.002$), and $28.3±3.0\%$; epicardial values were $12.3±0.4$ cm and $11.8±0.3$ (NS), and $3.7±2.4\%$, respectively. Diastolic and systolic septal wall thicknesses were $2.9±0.1$ and $3.6±0.1$ cm, respectively ($p<0.001$), and thickening was $23.0±1.3\%$. The corresponding free wall values were $2.2±0.1$ and $3.1±0.1$ cm ($p<0.001$), while thickening was $43.2±3.5\%$. The septum was significantly thicker than the free wall in both diastole ($p<0.001$) and systole ($p<0.001$), whereas thickening in the free wall was twice that of the septum ($p<0.001$). The diastolic mean wall thickness to short-axis ratio was $0.35±0.03$ and the corresponding systolic value was $0.64±0.07$. Values of mean diastolic dimensions; systolic dimensions and changes in dimension during systole are given in Tables 1-3.

**Determination of cardiac output with echocardiography ($Q_E$) and gas rebreathing ($Q_G$)**

Average heart rate was $56±5$ min$^{-1}$. Calculated EDV was $521±61$ ml or $1.05±0.61$ ml kg$^{-1}$ and ESV was $228±32$ ml or $0.46±0.83$ ml kg$^{-1}$, yielding an average SV of $293±42$ ml or $0.59±0.42$ ml kg$^{-1}$, and an ejection fraction of $55.8±3.6\%$. Thus the echocardiographically derived cardiac output ($Q_E$) was $16.1±2.5$ l min$^{-1}$ or $33±12$ ml kg$^{-1}$min$^{-1}$. In the 9 animals studied by the gas rebreathing procedure, the measured cardiac output ($Q_G$) values ranged from $12.0$ to $18.7$ l min$^{-1}$, providing a mean of
33±2 ml kg⁻¹ min⁻¹. During inert gas rebreathing heart rate was 58±5 min⁻¹ and the calculated SV was therefore 278±42 ml.

An overview of calculated variables from echocardiographic data is presented in Table 4.

**Systemic vascular resistance**

In the six giraffes where we obtained simultaneous recordings of MAP, P_RA and Q (234±12 mmHg, 5±2 mmHg and 15 ± 1 l min⁻¹, respectively), we calculated SVR to be 16 ± 1 mmHg l⁻¹ min⁻¹.

**Wall stresses and net external work performed by the left ventricle**

Circumferential- and meridional wall stresses were 7.83±4.66 kPa and 7.83±2.28 kPa respectively. Left ventricular work averaged 7.2±1.1 Watt (W) based on a ΔP of 229±14 mmHg, and a Q of 15.0 l min⁻¹. Heart mass was 2.68±0.6 kg corresponding to 0.53±0.05 % of body mass. Normalized to body mass, the net external work of the heart was 0.29 W kg⁻¹.

**Corresponding human values**

Typical corresponding values for a healthy 80 kg human with a heart rate of 70 beats per min would be an EDV of 150 ml or 1.88 ml kg⁻¹, an ESV of 70 ml or 0.88 ml kg⁻¹, a SV of 80 ml or 1 ml kg⁻¹, an ejection fraction of 53.3 %, and a cardiac output of 5.6 l min⁻¹ or 70 ml kg⁻¹ min⁻¹. With a mean arterial pressure of 80 mmHg, a systolic pressure of 110 mmHg and a right atrial pressure of 5 mmHg, the systemic vascular resistance would be 13.4 mmHg l⁻¹ min⁻¹ and circumferential- and meridional wall stresses would be 8.91 kPa and 2.90 kPa respectively.

**Diffusion tensor imaging**

An example of the tracking of the ventricular myocytes in the giraffe heart is shown in Figure 4 where we also inserted a similar visualisation of the cardiomyocytes of the pig heart for comparison. The principal myocardial architecture of the giraffe left ventricle, *i.e.* the so-called helical angle distribution (the inclination of the cardiomyocyte tracks relative to the equatorial plane of the left ventricle) as well as the pattern of myocardial pathways did not reveal any obvious differences compared to that of other mammals (Scollan et al., 1998; Smerup et al., 2009).

**Discussion**

Our *in vivo* echocardiography revealed that the giraffe heart, compared to that of other mammals, is characterized by a small left ventricular cavity and hence a small ventricular radius as well as a comparatively large left ventricular myocardial wall thickness, a notion previously been from post mortem observations (Mitchell and Skinner, 2009; Østergaard et al., 2013). Since we also
confirmed the conspicuously high MAP and the associated high intraventricular pressures in the
giraffes, our findings support the hypothesis that the combination of thick left ventricular wall and
a low radius of the left ventricular cavity allow for a normal mammalian myocardial wall stress in
the giraffe heart. In fact, the calculated wall stress of the left ventricle in the giraffes is virtually
identical to that reported for other mammals (Seymour and Blaylock, 2000). The low SV is
corroborated by the independent measures of low CO using the inert gas-rebreathing technique,
and it is clear therefore that the normalisation of ventricular wall stress by the low radius ventricle
may constrain oxygen delivery by the cardiovascular system.

Based on our own preliminary trackings of the cardiomyocytes in the giraffe left ventricle, there
does not appear to be any significant principal differences in the myocardial architecture between
the giraffe and other mammals (Nielsen et al., 2009; Smerup et al., 2009). Therefore, there is no
indication that giraffes have evolved cardiomyocytes generating excessive force or other peculiar
adaptations; instead, the ability to develop a sufficiently high pressure for cerebral perfusion in
the standing position can merely be ascribed to the thick myocardial wall and the small radius. We
found that the giraffe meridional and circumferential wall stresses were identical. This is
interesting since the former value normally exceeds the latter, and this may indicate that giraffe
left ventricles have slightly altered myocardial architecture that possibly serves to redistribute
myocardial stresses differently during cardiac contraction in comparison to the myocardium of
other species, which exhibit a lower ventricular wall thickness to cavity diameter ratio (WT/D).

Indeed, the altered WT/D ratio in the adult giraffe seems to be an example of a beneficial
physiological adaptation to a naturally high MAP, caused by a high SVR, which is in itself an
adaptation to the perfusion requirements of the brain. Thus, although the thick ventricular wall
resembles the pathophysiological changes during acquired ventricular hypertrophy in response to
aortic stenosis or hypertension in humans (Grossman et al., 1975; Hood et al., 1968; Sandler and
Dodge, 1963) there is no indication of the secondary myocardial fibrosis in giraffes that inevitably
accompanies the acquired left ventricular hypertrophy observed in human disease. It is also
noteworthy that new-born giraffes have a myocardial wall thickness relative to ventricular
diameter similar to other mammals, such that the ventricular wall thickening seems to arise as
MAP increases with neck length (Mitchell and Skinner, 2009). Because the ventricular remodelling
develops in response to increased afterload as the giraffe grows taller and because total
myocardial volume of adult giraffes resembles that of similar-sized mammals, we suggest that the
term concentric eutrophy be used for the normal physiological state of the adult giraffe
myocardium. The low cardiac output of giraffes alleviates the influence of the high mean arterial
pressures on the workload on the heart. Our estimation of cardiac workload in the giraffe (0.29 W
kg\textsuperscript{-1} heart) is very similar for example to the workload of the healthy human heart (0.36 W kg\textsuperscript{-1} heart).

Our echocardiography also reveals a normal mammalian ejection fraction, and hence low ventricular volumes, \textit{i.e.} EDV, ESV and SV, being almost half of those in similar-sized mammals. This is illustrated in Figure 5 depicting reported stroke volumes in mammals (Seymour and Blaylock, 2000) as a function of body mass. The calculations of volumes based on echocardiography relies upon the assumption that the left ventricle is shaped like a prolate hemi-ellipsoid, but the low volumes were also confirmed independently by the measurements using the inert gas rebreathing technique. Determination of cardiac output by gas clearance in the lungs over multiple heartbeats and is therefore methodologically distinct from echocardiographic methods relying on beat-to-beat changes in ventricular volumes. Thus our study provides strong evidence for a considerable lower cardiac output in giraffes than in other similar-sized mammals. In the literature, we are aware of only two earlier studies of cardiac output, providing data from a total of eight measurements in five specimens, have reported cardiac output in giraffes, but several of the values were not corrected for body mass. Goetz (1960) used both indicator-dye dilution and the direct Fick methods in one ill and three healthy giraffes (values are reported for three of the animals). The authors described difficulties with the dye-dilution technique, but obtained cardiac output measurements of 48 and 78 ml kg\textsuperscript{-1} min\textsuperscript{-1} using direct Fick in the two individuals where body mass was estimated (500 and 455 kg, respectively). In the only other study, Linton et al. (1999) were surprised to measure a cardiac output of only 20 l min\textsuperscript{-1} (equivalent to 25 ml kg\textsuperscript{-1} min\textsuperscript{-1}) in an 800 kg giraffe using a lithium dilution technique. This value fits remarkably well with our measurements.

Our study also confirms that systemic vascular resistance (SVR) of giraffes is considerably higher than that of other similar-sized mammals. Given the low cardiac output, the high SVR is required to support the high MAP necessary to perfuse the brain, but our study does not provide insight to the specific mechanisms underlying the high resistance. Previous studies have reported thick blood vessel walls with high wall to lumen ratio (\textit{e.g.} Hargens, 1988; Keen and Goetz, 1957; Kimani et al., 1991; Østergaard et al., 2011; Petersen et al., 2013), but there is clearly a need to study in more detail the resistance vessels throughout the vasculature.

The myocardial remodelling clearly seems adaptive to the high MAP required for cerebral perfusion, but the resultant decrease in stroke volume (SV) obviously impose a potential limitation to systemic oxygen delivery. The rate of oxygen consumption of anaesthetised giraffes resembles that of similar-sized mammals (Langman et al., 1982), and the low SV is in any event unlikely to constrain resting metabolism as an increased arterial-venous oxygen extraction could suffice. In
free-moving awake giraffes, van Citters et al. (1969) reported heart rate to increase from around 40 min\(^{-1}\) in undisturbed quietly-standing giraffes to maximum values of 175 min\(^{-1}\) during galloping when actively chased on the savannah. It remains to be determined whether this more than four-fold rise in heart rate is attended by altered SV, but the thick ventricular wall probably lowers ventricular compliance and it could be speculated to constrain the ability for the ventricle to alter SV. Thus, the low SV probably persists during exercise and constrain aerobic performance and hence limit the maximal aerobic running speed. However, the long legs of giraffes appear to reduce energy expenditure required for transport (Pontzer, 2007). Thus, as SV became increasingly constrained by concentric eutrophy of the ventricle in response to the progressive evolution of a longer neck (i.e. increasing the vertical distance between the heart and head and thus requiring higher MAP), the requirements on oxygen delivery during locomotion were probably alleviated, as the legs also got longer. Clearly this speculation needs to be supported by e.g. measurements of field metabolic rate, for example by double-labelled water, and the associated cardiovascular responses to estimate cost of locomotion in free ranging giraffes.

It can be calculated that a “perfect left ventricle”, i.e. a pumping chamber that achieves the high MAP of giraffes and thus retains the beneficial ratio of radius versus wall thickness reported here, while still being able to generate a cardiac output per body mass unit comparable to other mammalian species would have an EDV of 1060 ml and a SV of 583 ml, which is approximately twice the measured values. The cavity radius would be 4.7 cm and the myocardial wall thickness 3.3 cm. Since it is not straightforward to calculate the total mass of this hypothetical pump, it can only be speculated that the energy cost of such an organ would likewise surmount the average mammalian value by a factor two or three.

The main limitation to the present study is the use of linear dimensions measured with echocardiography to determine left ventricular volumes by assuming the fairly simple prolate hemi-ellipsoidal geometry. This method has obviously not been validated since our study is the first to report the use of echocardiography on the giraffe heart, and since no gold standard for measurements in this species exist. By virtue of the same argument we did not use Simpson’s method (Folland et al., 1979) or other indirect methods for volume assessment.

In conclusion, our study supports the notion that relative myocardial mass is fairly invariant amongst mammals. The phenotypical adaptations to the high arterial pressures in giraffes have been achieved by evolving a low volume, low flow pump that is suitable to maintain cerebral perfusion, but imposes limitations on cardiac chamber size and stroke volume and possibly on maximum sustainable rate of oxygen consumption.
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Competing Interests

The authors declare no competing financial interests.

Author contributions

All authors contributed to the idea, conception, experimental design, experiments or analysis of the data. M.S., M.D. and T.W. collated the data and wrote the manuscript. All authors approved and contributed to the final version.

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Figure 1. Organization of the giraffe cardiac mass. Shown in panel A are computer-generated images of two hearts with identical cardiac mass; in blue is shown a heart with the typical mammalian organization of cardiac tissue and in red is shown a heart with organization similar to that of the giraffe. Note how the giraffe heart has both a thicker ventricular wall and a smaller cavity. In panel b is shown a short axis view through the giraffe heart at the level of the papillary muscles. Right ventricle (RV), intraventricular septum (IVS), left ventricle (LV) and papillary muscle (PM).
Figure 2: *In-vivo* intracardiac echocardiography showing long Axis view “4-chamber view” of the giraffe heart. The probe is located in the right atrium (*). Shown are images from the same heart cycle in one giraffe in end diastole (A) and end systole (B). Red marker on ECG-trace shows temporal relation to the cardiac electrical activity. Right ventricle (RV), intraventricular septum (IVS), left ventricle (LV) and left ventricular wall (LVW).
Figure 3. An original recording of arterial pressure as well as the pressures within the left and the right ventricle (LVP and RVP, respectively) of an anaesthetised giraffe.
Figure 4. Diffusion tensor imaging (DTI) of the left ventricles of a giraffe (A) on the left and that of a pig (B) on the right. Essentially this technique allows for visualization of the orientation of the cardiomyocytes. There does not appear to be any significant differences in the myocardial architecture compared to other mammals. Tracks are arbitrarily colored to allow for easier differentiation of the orientation of the diffusion direction relative to the myocardium. The colors are therefore merely a visual aid and do not represent any anatomical or physiological properties.
Figure 5. Measured stroke volume (ml) plotted as function of total body mass (kg) in various extant mammal species, as reported Seymour & Blaylock, 2000, (▲). The full line indicates the semi log regression line calculated on the basis of these values, stippled line indicates the calculated 95% confidence interval. Shown in red (●) is the corresponding value for Giraffes reported in the present study.
References


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<td>MAP</td>
<td>mean arterial blood pressure</td>
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<td>LVP</td>
<td>left ventricular pressure</td>
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<td>ΔLVP</td>
<td>change in left ventricular pressure</td>
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<td>systolic endocardial short-axis diameter</td>
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<td>systolic endocardial long-axis diameter</td>
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<td>r</td>
<td>midwall radius of the left ventricle</td>
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<tr>
<td>Wt</td>
<td>systolic wall thickness of the left ventricle</td>
</tr>
<tr>
<td>EDV</td>
<td>end diastolic volume</td>
</tr>
<tr>
<td>ESV</td>
<td>end systolic volume</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>Q</td>
<td>cardiac output</td>
</tr>
<tr>
<td>CWS</td>
<td>systolic circumferential wall stress</td>
</tr>
<tr>
<td>MWS</td>
<td>systolic meridional wall stress</td>
</tr>
<tr>
<td>W</td>
<td>work of the heart</td>
</tr>
<tr>
<td>RVP</td>
<td>right ventricular pressure</td>
</tr>
<tr>
<td>SVR</td>
<td>systemic vascular resistance</td>
</tr>
<tr>
<td>PRA</td>
<td>right atrial pressure</td>
</tr>
</tbody>
</table>
### Table 1 - Mean diastolic dimensions

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-axis (cm)</td>
<td>18.2 ± 0.3</td>
</tr>
<tr>
<td>Endocardial short-axis (cm)</td>
<td>7.3 ± 0.5</td>
</tr>
<tr>
<td>Epicardial short-axis (cm)</td>
<td>12.3 ± 0.4</td>
</tr>
<tr>
<td>Septum (cm)</td>
<td>2.9 ± 0.1</td>
</tr>
<tr>
<td>Free wall (cm)</td>
<td>2.15 ± 0.04</td>
</tr>
<tr>
<td>Mean wall thickness to short-axis ratio</td>
<td>0.35 ± 0.03</td>
</tr>
</tbody>
</table>

### Table 2 - Mean systolic dimension

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-axis (cm)</td>
<td>15.5 ± 0.3</td>
</tr>
<tr>
<td>Endocardial short-axis (cm)</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>Epicardial short-axis (cm)</td>
<td>11.8 ± 0.3</td>
</tr>
<tr>
<td>Septum (cm)</td>
<td>3.55 ± 0.06</td>
</tr>
<tr>
<td>Free wall (cm)</td>
<td>3.08 ± 0.08</td>
</tr>
<tr>
<td>Mean wall thickness to short-axis ratio</td>
<td>0.64 ± 0.07</td>
</tr>
</tbody>
</table>

### Table 3 - Systolic changes

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-axis shortening (%)</td>
<td>14.9 ± 0.3</td>
</tr>
<tr>
<td>Endocardial short-axis shortening (%)</td>
<td>28.3 ± 3.0</td>
</tr>
<tr>
<td>Epicardial short-axis shortening (%)</td>
<td>3.7 ± 2.4</td>
</tr>
<tr>
<td>Septal thickening (%)</td>
<td>23.0 ± 1.3</td>
</tr>
<tr>
<td>Free wall thickening (%)</td>
<td>43.2 ± 3.5</td>
</tr>
</tbody>
</table>
Table 4 – Mean calculated parameters

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>per kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>End diastolic volume (ml)</td>
<td>521±61</td>
<td>1.05±0.61</td>
</tr>
<tr>
<td>End systolic volume (ml)</td>
<td>228±32</td>
<td>0.46±0.35</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>293±42</td>
<td>0.59±0.42</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.8±3.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>16082±2544</td>
<td>33.2±4.40</td>
</tr>
<tr>
<td>Circumferential wall stress (kPa)</td>
<td>7.83±1.76</td>
<td>N/A</td>
</tr>
<tr>
<td>Meridional wall stress (kPa)</td>
<td>7.83±0.86</td>
<td>N/A</td>
</tr>
</tbody>
</table>