Left Ventricular Hypertrophy Induced by Reduced Aortic Compliance

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Cardiac hypertrophy · Hemodynamics · Reduced aortic compliance

Abstract
Aim: It was the aim of this study to investigate the long-term effects of reduced aortic compliance on cardiovascular hemodynamics and cardiac remodeling. Method: Sixteen swine, divided into 2 groups, a control and a banding group, were instrumented for pressure and flow measurement in the ascending aorta. Teflon prosthesis was wrapped around the aortic arch in order to limit wall compliance in the banding group. Hemodynamic parameters were recorded throughout a 60-day period. After sacrifice, the mean cell surface of the left ventricle was documented. Results: Banding decreased aortic compliance by 49 ± 9, 44 ± 16 and 42 ± 7% on the 2nd, 30th and 60th postoperative day, respectively (p < 0.05), while systolic pressure increased by 41 ± 11, 30 ± 11 and 35 ± 12% (p < 0.05), and pulse pressure by 86 ± 27, 76 ± 21 and 88 ± 23%, respectively (p < 0.01). Aortic characteristic impedance increased significantly in the banding group. Diastolic pressure, cardiac output and peripheral resistance remained unaltered. The mean left ventricular cell surface area increased significantly in the banding group. Conclusions: Acute reduction in aortic compliance results in a significant increase in characteristic and input impedance, a significant decrease in systemic arterial compliance and a subsequent increase in systolic and pulse pressures leading to left ventricular hypertrophy.

Introduction

The proximal aorta is a highly compliant vessel, which reduces left ventricle (LV) workload and damps the propagated pressure wave [1]. Aortic reconstruction with a prosthetic noncompliant graft reduces this compliance and may have an adverse effect on cardiovascular hemodynamics, which in turn may lead to hypertension, cardiac hypertrophy and ischemia, the development of vessel wall disease and thrombosis formation [2–8]. Furthermore, the different radial dilation of the prosthesis and the host vessel leads to stress concentration in the sutures of the anastomoses, which may lead to fatigue failure of
the suture line and tearing of the host artery resulting in anastomotic aneurysm formation [7].

Clinical observations have documented LV hypertrophy after an ascending-abdominal aorta bypass for thoracoabdominal aneurysm, most likely a result of increased aortic input impedance [9]. Later reports correlated LV hypertrophy seen after proximal or long bypass procedures with noncompliant grafts, with increased characteristic impedance, decreased Windkessel effect of the proximal aorta and increased systolic wall stress [4, 5, 10, 11]. This ‘stiffening’ of the vasculature has been shown to augment cardiac dysfunction and ischemia due to coronary occlusion by tightening the link between cardiac systolic performance and myocardial perfusion [12].

This experimental study was undertaken to investigate the long-term effects of acutely reduced aortic compliance, such as after proximal aortic reconstruction, on hemodynamics and cardiovascular remodeling. This article supplements and expands previous reports not only by studying acute findings from open- or closed-chest animals, but by studying long-term results. Furthermore, we surgically reduced compliance in a manner that preserves the natural geometry of the arterial tree.

**Animals and Method**

**Surgical Instrumentation**

General surgical preparation and instrumentation have previously been described in detail [2]. Briefly, under general anesthesia and using aseptic technique, 16 conditioned Yucatan miniature swine of either sex (mean weight 26 ± 4 kg) underwent a left thoracotomy. The heart, the aortic arc and great vessels were exposed and a calibrated pressure transducer (Konigsberg Instruments Inc., Pasadena, Calif., USA) was implanted in the ascending aorta 0.5 cm above the coronary arteries to obtain aortic pressure measurements. An appropriately sized transit time ultra-
sonic flow probe (Transonic System Inc., Ithaca, N.Y., USA) was placed around the ascending aorta for aortic blood flow measurement just above the aortic pressure transducer (fig. 1). Both the pressure sensor and the flow probe were fixed into place in order to be used for the entire length of the experiment. All instrumentation cables were exteriorized through the 6th intercostal space, fixed on the back of the animal and were routed to a computer data processor where a recording was made as a control condition (reported as ‘after instrumentation’). All signals were digitized, treated and further analyzed with the IOX 1568 laboratory analysis program (EMKA Technologies, Paris, France). The 16 miniature swine were divided into 2 equal groups, a sham-operated group (control group) and a banding group. Both groups underwent the same surgical instrumentation procedure, as described above. In the banding group, the ascending, transverse and the beginning of the descending aorta were band- ed using 3 strips of Teflon prostheses (fig. 1). One strip was placed around the ascending aorta, between the flow probe and the innominate artery (approximately 1 cm wide), a second strip (0.6–0.8 cm) between the innominate and the left subclavian artery (pigs have only 2 branches arising from the aortic arc), and a third strip, approximately 1.3 cm, around the proximal de- scending aorta. Bands were snugly fit around the aorta to reduce its expansion during the cardiac cycle, and thus to reduce compliance. The band did not constrict the aorta, and thus did not create a pressure drop. This was verified after temporarily introduc- ing a calibrated intra-arterial pressure needle catheter into the descending aorta distally to the banded area and comparing the pressure curve with that obtained from the Konigsberg pressure sensor.

On the 2nd, 30th and 60th postoperative day (POD), the ani- mals were anesthetized and mechanically ventilated similarly to the day of operation, and another set of data recordings were con- ducted.

To balance a possible effect on baroreceptors located on the aortic wall, the animals in the control group underwent the same extensive exposure of the aortic arch as the animals in the banding group. Furthermore, the presence of an intact autonomic reflex was assessed intraoperatively by testing for the presence of heart rate response to varying preload pressures after temporar- ily occluding and releasing the inferior vena cava.

The experimental protocol was approved by the Medical Fac- ulty of the Geneva Animal Ethics Committee as well as by the Cantonal Veterinary Office and conformed to the ‘Guide for the care and use of laboratory animals by the US National Institutes of Health’ (NIH Publication No. 85-23, revised 1996).

**Hemodynamic and Arterial Parameters**

Arterial blood pressure and flow were directly measured by the implanted pressure transducer and flow probes. The read- ings were relayed to the computer, where the IOX software pro- gram recorded the measurements in the data bank with a sam- pling frequency of 500 Hz. Using the blood pressure and flow inputs, the software calculated and registered the heart rate, pulse pressure, systolic pressure, diastolic pressure and mean blood pressure from the pressure input signal and the stroke volume, the maximum flow, minimum flow and mean flow, as well as the cardiac output from the flow input signal. All parameters of each animal were calculated for 15–20 consecutive heartbeats to obtain an average value. Average pressure and flow waves were transformed in the Fourier domain, and aortic input impedance was calculated as the ratio of pressure to flow for each harmonic. Peripheral resistance was calculated as mean aortic pressure over mean flow. Characteristic impedance was obtained by av- eraging the impedance moduli between the 4th and 10th harmonic.

Total arterial compliance was estimated by the pulse pressure method introduced by Stergiopulos et al. [13, 14]. The pulse pres- sure method is based on the fact that the pulse pressure of the arterial wave is very well ‘captured’ by the 2-element Windkessel model, due to the extremely good impedance modulus characteristics of this model at the low frequency domain.

**Histology Sample Preparation and Image Acquisition**

Upon completion of the last measurements, the animals were sacrificed and the heart was extracted. Transversal sections of the LV wall opposite to the right ventricle were made. The samples were placed in formaldehyde for at least 24 h before being embed- ded in paraffin. Samples in paraffin blocks were cut into 3-μm sections that were stained with hematoxylin-eosin.

Sections were observed on a Zeiss Axiophot photomicroscope (Carl Zeiss, Oberkochen, Germany). Ten randomly selected areas of the section were photographed with a highly sensitive Photon- ic Coolview 3CCD color camera (Photonic Science, Saint Etienne de Saint Geoirs, France). It should be noted that 10 pictures usua- lly cover almost the whole sample surface. Then, the images were analyzed using the KS400 2.0 software (Kontron Elektronik, GmbH, Eching, Germany). Cell structures were selected on the basis of the pixel intensity values in each color channel. Cell nuclei were selected and counted (blue-black colors). Then, the total sur- face of the cell section was selected (pink color). The mean cell surface was obtained by dividing the total cell surface of the ana- lyzed area by the number of nuclei contained in this area. Cell surfaces were obtained in pixels and then converted in square mi- crometers depending on the magnification used to acquire the images. The magnification used to examine and photograph the specimens was ×40.

**Statistical Analysis**

Grouped data are presented as means ± SEM. The unpaired Student’s t test was used for statistical comparison of the control group with the animals in the banded group. A paired t test was used for statistical comparison of the changes in hemodynamic parameters of the animals within the same group. Only p values <0.05 were considered significant.

**Results**

The decrease in total arterial compliance, after band- ing, caused changes in the morphology of the pressure curves that resulted in pulse pressure amplitude increase (fig. 2) and a partial loss of the aortic Windkessel func- tion. Following banding, the shape of the pressure wave is characterized by a late systolic increase. On the contr- ary, flow curve morphology was unaltered after band- ing.
Hemodynamic and Arterial Parameters

Comparison of mean values of all hemodynamic and arterial parameters during instrumentation and postoperatively for the control group showed no statistical differences. Comparison between the control and the banded animal groups before banding showed no statistical differences in all hemodynamic and arterial parameters either. This confirms that instrument implantation did not alter arterial hemodynamics (table 1).

Aortic banding decreased compliance from $0.49 \pm 0.05$ to $0.25 \pm 0.03$ ml/mm Hg on the 2nd POD after banding ($p = 0.003$). Even though compliance recovered slightly on the 30th and 60th POD (0.28 $\pm$ 0.02 and 0.29 $\pm$ 0.03 ml/mm Hg, respectively), the difference remained statistically significant when compared with the prebanding state ($p = 0.01$ and 0.001, respectively) as well as when compared with the control group (table 1). Peripheral arterial resistance was unaffected by banding of the
The mean values (± SEM) are presented for the control animals (n = 8) and the banded animals (n = 8) for each parameter. Day 0 represents the values recorded after instrumentation of the animals in both groups, whereas measurements immediately after banding (only for the banding group) on day 0 are not depicted in the table.

a p < 0.05, comparison between the control and the banded group on the respective day (column).
b p < 0.05, comparison within the banded group, between the value given in the ‘after instrumentation’ column (before the banding state) versus the value of the respective day.

The input impedance modulus increased significantly over the entire harmonic range (fig. 3a). In consequence, this led to a significant increase in aortic characteristic impedance, from 2.65 ± 0.84 mm Hg/(ml/s) in the control group to 5.96 ± 1.39 mm Hg/(ml/s) in the banding group on the 60th POD (p < 0.005; fig. 3b).

Banding increased the systolic pressure from 86.3 ± 4.8 to 121.6 ± 6.8 mm Hg on the 2nd POD and remained elevated thereafter (p < 0.05; table 1). Pulse pressure increased from 23.5 ± 2.2 mm Hg prior to banding to 43.7 ± 4.4 mm Hg at 2 days postoperatively and remained as high throughout the 2-month period (p < 0.01).

The mean blood pressure increased after banding from 74.3 ± 4.6 to 98.3 ± 6.6 mm Hg on the 2nd POD (p = 0.01), but later slightly decreased to 89.2 ± 6.6 mm Hg on the 30th and to 94.4 ± 9.3 mm Hg on the 60th POD, making the increase with respect to control nonsignificant (p = 0.11 and 0.16, respectively). Note that there is a difference in heart rate, though nonsignificant, between the control group and the banded group, even on the day of instrumentation (before banding) when the 2 animal situations should be similar (111 ± 7 vs. 91 ± 5 beats/min), which is probably incidental. After banding, we observed an initial marginally significant increase in heart rate on the 2nd POD (p = 0.05), which returned to prebanding levels thereafter. This increase may be a result of some sort of compensatory mechanism in response to compliance reduction [2]. Diastolic pressure, cardiac output and stroke volume remained unchanged after banding (table 1).

LV Hypertrophy

Staining the samples with hematoxylin-eosin revealed an increase in the cell area in the banding group (fig. 4). The mean cell section area in the control group was 251 ± 12 µm², and 351 ± 17 µm² in the banded group (fig. 5). We observed a significant increase of 40% in the cell area in the banding group (fig. 4).

Animal Body Weight

The initial animal body weight was 26.0 ± 1.6 kg for the banding group and 26.1 ± 1.6 kg for the control group. At sacrifice, body weights were 30.1 ± 1.9 and 29.2

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Cardiac Hypertrophy after Compliance Reduction
± 1.9 kg for the banding and control group, respectively. This particular breed of swine (Yucatan miniature pigs) was chosen for our experiment because they neither grow rapidly nor does their body weight usually go above 35 kg. This restricted animal growth characteristic limits possible size alterations in the swine’s aorta as well as possible subsequent constricting effects of the aortic bands (bANDING GROUP). Furthermore, as seen in table 1, all hemodynamic parameters after day 2 remained consistent in both groups throughout the 8-week study period, thus implying that the aortic anatomy remained practically unaltered.

**Discussion**

We have performed an aortic banding procedure to acutely reduce proximal aortic compliance in a swine model in order to evaluate its long-term effect on vascular hemodynamics and its impact on cardiac remodeling. Banding of the proximal aorta reduced total systemic arterial compliance by 40–50%, providing evidence that the proximal aorta is the major contributor to total arterial compliance and is an important determinant of cardiac afterload. In turn, reduction in compliance led to an increase in systolic and pulse pressure while peripheral re-
Compliance remained unaltered. Furthermore, the acutely reduced aortic compliance resulted in a 40% increase in LV mass after 60 days.

Banding resulted in an approximately 50% decrease in arterial compliance and in a substantial increase (225%) in the characteristic impedance of the proximal aorta. These results are consistent because characteristic impedance is inversely proportional to the square root of the local area compliance of the proximal aorta. To yield the observed 225% increase in characteristic impedance, proximal aortic area compliance must have been decreased by 80%, a plausible outcome of the snug fit of the inelastic Dacron band. Taking into account that proximal aorta accounts for about 60% of the total systemic compliance [2, 15], an 80% reduction in proximal aortic compliance would lead to an 80%-60% = 48% reduction in the total systemic compliance, which indeed is the observed event.

Loss in total systemic compliance leads to augmentation in pulse pressure, due to reduction in Windkessel function [2, 13, 16]. Mechanistically, this can be attributed to increased wave speed, and thus earlier arrival of reflected waves [2], but also to the increase in input impedance modulus, as was indeed the case in this experiment (fig. 3a). An increase in input impedance modulus together with a non-change in cardiac output and aortic flow waveform, as was also the case in our experiments, means that each pressure harmonic will be augmented in amplitude. This leads to augmented pulse pressure. The increase in pulse pressure can also be explained without reference to reflected waves, but via the increase in characteristic impedance [17, 18]. In early systole, well before reflected waves arrive from the periphery, systolic pressure increase is proportional to early systolic flow wave times characteristic impedance. Since flow remains the same and characteristic impedance increases, early systolic pressure will also increase, leading to augmented pulse pressure. Our results support all phenomena described above, which are all likely to be contributing to the observed systolic and pulse pressure augmentation.

Previous studies [2, 9, 12, 16, 19, 20] have consistently shown that reducing compliance leads to an increase in systolic and pulse pressure, but their findings have varied with regard to the other variables measured. Our study differs from the previous studies in 2 aspects: first, it reports long-term data after nonstenotic banding of the aorta and, second, the reduction in aortic compliance was done in a manner preserving the native aortic flow and geometry. It has been reported that in an end-to-side graft anastomosis, decreased graft compliance leads to a substantial increase in the maximum anastomotic mean stress resulting in anastomotic intimal thickness [8, 21]. By banding the aorta in our experiment and not replacing it with a synthetic graft, aortic wall injury, changes in wall shear stress and flow disturbances at the suture sites were avoided. Furthermore, this method avoided the development of new reflection sites at the suture line, thus limiting the possibility of other factors, except aortic stiffening, contributing to the increase in systolic pressure.

The total hydraulic power developed by the LV to propel the blood through the systemic circulation depends not only on the ability of the LV to do external work, but also on the properties of the arterial tree into which the blood is ejected [22]. The LV is generally thought to adapt to sustained arterial hypertension by developing concentric hypertrophy [23]. As a first compensatory ventricular response to a chronic pressure overload, wall thickness increases to normalize the wall stress, and LV dilatation represents a late transition toward myocardial failure. Although evidence has accumulated as to the role of hemodynamic load and myocardial contractile state [24], little information is available about the influence of changes of arterial properties, such as with ageing or after aortic reconstructive surgery, on the development of LV hypertrophy and their possible pathophysiological mechanisms.

Total arterial compliance and peripheral vascular resistance are the major physiological parameters characterizing cardiac afterload. The aorta is a compliant vessel and acts as an elastic reservoir. It absorbs part of the hydraulic energy imparted to the blood during systole to be

![Fig. 5. Mean cell section areas of the LV sections from the control and banded groups.](image-url)
released later during diastole, thus converting the pulsatile flow from the heart into a more steady flow in the arterial system, maintaining a constant distal flow. Replacing the aorta with a noncompliant vascular prosthesis changes the elastic properties of the arterial system, resulting in a loss of arterial distensibility, and thereby interferes with the ventriculoarterial coupling [25, 26]. Most currently available prosthetic grafts are stiff, with little differences between graft materials. It has been estimated that a woven Dacron graft is approximately 170 times stiffer than the natural aorta [3]. The apparent stiffness of synthetic prostheses should theoretically make them less satisfactory as arterial replacements because of the loss of compliance, but also because of the resulting increase in pulse wave velocity giving rise to higher pulse pressure and increased wave reflections [2]. The compliance mismatch between the graft and the artery imposes excessive stresses on the suture lines, resulting in intimal hyperplasia, suture fatigue or anastomotic aneurysms [8, 21, 27]. Furthermore, the heart interacts with the altered arterial system after banding and, by means of its own adaptation to the altered afterload, contributes to the new aortic and pressure waveforms.

In the prospective Framingham Heart Study, LV mass was associated with all outcome events in both men and women [28]. Persons with LV hypertrophy are twice as likely to die of coronary heart disease and other diseases of the heart, after adjustment for hypertension and other cardiovascular risk factors. It seems that our experimental model simulates the pathophysiological state found in patients with isolated systolic hypertension where systolic blood pressure is increased, whereas diastolic blood pressure is not. This accounts for the increase in pulse pressure that seems to be evolving into a very important predictor of cardiovascular morbidity and mortality [29–31] and stroke [32].

The noncompliant arterial tree leads to increased systolic pressure without significantly affecting the diastolic pressure, resulting in a widened pulse pressure. Atherosclerosis reduces arterial compliance by stiffening the arterial wall. Furthermore, increased blood pressure may increase vessel wall damage, resulting in even further arterial stiffening and compliance reduction. The noncompliant arterial wall may be subjected to increased pulsatile pressure and intraluminal stress. Recently, Pini et al. [33] reported that elevated pulse pressure was an independent predictor of LV hypertrophy among a cohort of patients >65 years of age. In our study, both systolic and pulse pressure increased following the decrease in compliance, resulting in an increase in LV mass. It is evident that the heart interacts with the altered arterial system after banding triggered an increase in LV mass in order to compensate for the increase in myocardial stress. The energy to maintain a forward blood flow in the aorta is given by mean pressure generated by the LV. From the concept that the pulsatile component of blood pressure loses energy during vascular pulsation [22], widened pulse pressure becomes a cause of energy loss for maintaining the forward blood flow. Therefore, the LV must generate excessive energy to maintain the cardiac output through an unchanged peripheral resistance. This results in an increase in LV work, consequently leading to hypertrophy [9]. As previously reported [9, 10], the use of woven Dacron grafts for extra-anatomic aortic bypass procedures may result in LV hypertrophy due to the significant systolic pressure increase from the loss of the natural aortic Windkessel property. In our study, we observed a significant increase in LV mass in the banded group compared with the control group (fig. 4, 5). Thus, the decrease in aortic compliance observed after arterial replacement with vascular prosthesis leads to isolated systolic hypertension and, subsequently, to LV hypertrophy. Cardiovascular remodeling due to increased systolic and pulse pressure is not confined to the heart alone. Boutouyrie et al. [34] demonstrated that during long-term antihypertensive treatment, regression of carotid artery wall hypertrophy was dependent on reduction of pulse pressure, confirming a relationship between pulse pressure and carotid remodeling. It seems that the heart and the arterial system are interlinked, and any disturbance in the balance between the two will lead to a new equilibrium in terms of hemodynamics and cardiac function affecting both systems.

In conclusion, about half of the total systemic arterial compliance is located in the proximal thoracic aorta. A decrease in systemic arterial compliance, as for example after reconstruction of the proximal aorta with noncompliant grafts, results in a significant increase in systolic and pulse pressure as well as in LV hypertrophy. The development of more compliant prostheses, which match the host artery compliance, is expected to reduce the hemodynamic changes induced after their implantation.

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References


