The effects of left ventricular stretch versus cavity pressure on intramyocardial pressure

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Abstract

Objective: Since muscles, vessels and interstitial spaces are in close physical proximity in the heart wall, interstitial (i.e., intramyocardial) pressure (IMP) should be affected by the stresses of the vessels and/or the muscular tissue surrounding the interstitial spaces. Thus, we tested the hypothesis that increasing the stresses or stiffness of the surrounding tissues by muscle contraction or stretching—produced externally by stretching the LV cavity or internally by increasing coronary perfusion pressure—has a greater effect than LV cavity pressure per se on IMP. Methods: In isolated rabbit hearts we measured IMP with small (\(< 10 \ \mu\text{m diam.}\)) glass micropipettes while stretching the vessels (by changing coronary perfusion pressure) and the wall (by inflating a balloon in the left ventricle) during the passive state as well as during barium contracture. Results: With LV cavity pressure equal to 0 (balloon open to air) or equal to 30 mmHg, a 20 mmHg increase in perfusion pressure increased IMP by 3.6 and 5 mmHg, respectively, in the passive state and by 7.6 and 7.9 mmHg, respectively, in the contracted state. This 30 mmHg increase in LV pressure produced a significant but small (3–5 mmHg) increase in IMP in the passive state but no effect in the contracture state. Conclusions: These results can be explained by a unifying concept in which stretching of the tissues surrounding the interstitial spaces—produced externally by increasing ventricular cavity size or internally by pressurizing vessels—but not LV cavity pressure per se is the major determinant of IMP. © 1997 Elsevier Science B.V.

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1. Introduction

Detailed knowledge of the stresses acting within the heart wall and how these are affected by various interventions is crucial to our understanding of cardiac mechanics. The heart wall is a complex structure composed of more or less solid components (collagen fibers, cell walls etc.), freely mobile as well as less mobile fluids (in vessels, cells, and interstitial spaces), and gel-like spaces (glycosaminoglycans, etc.). Because all these constituents are in close physical proximity and are arranged in a complex 3-dimensional array, the stresses acting on one constituent can directly affect those acting on the other constituents.

Consider, for example, a simple membrane wherein the Laplace relationship predicts that the pressure distributions on either side of a membrane depend upon the tension and the geometry of the membrane. Changing the pressure will deform the membrane. Conversely, changing the tension in the membrane by, e.g., stretching will change the pressure distribution. For more complicated structures than simple membranes, these interactions depend on the various components of the stresses in the wall of the structure rather than the simple tension. By analogy, the pressure in an interstitial space is determined by the resultant of the components of the stresses in the walls of the structures surrounding the space. Although the stresses in the various solid portions of the tissue can be predicted, direct mea-
urement is beyond our capability [1]. In contrast, the fluid pressures in the vessels or interstitial spaces—i.e., the intramyocardial pressure (IMP)—should be more amenable to direct measurement [2–6]. Since this pressure is affected by the mechanics of the surrounding solid and vessels, it is presumed that measurements of IMP should provide some insight into the mechanics of the wall [4].

A common belief is that, because the left ventricular cavity pressure and the pressure surrounding the heart are the radial stress boundary conditions at the surfaces of the myocardial wall, IMP should be directly related to the cavity and external pressures [2,7–11]. Previous studies suggest, however, that IMP is not related to left ventricular cavity pressure in either systole or diastole [12,13]. In fact, as discussed above, since IMP should be the resultant of all the solid stresses in the structures surrounding the interstitial space, of which radial stress is only one component, IMP may not necessarily be related to cavity pressure. Rather, since the stress-strain properties of almost all soft tissues are such that stresses increase non-linearly with increasing deformation, any intervention that stretches the solid structures should affect IMP. We therefore hypothesize that stretching the tissue components in the LV wall, whether imposed by stretching the entire LV or by stretching the vessels in the wall, rather than left ventricular cavity pressure, is a major determinant of IMP. Likewise, an intervention that directly increases the solid stresses by increasing myocardial stiffness without necessarily deforming the tissue (e.g., muscle contraction) should also increase IMP. Thus, muscle contraction, along with tissue stretch, should be an important determinant of IMP.

The aim of the present study is to test the hypotheses that wall stretch and stiffness rather than ventricular pressure is the major determinant of IMP. IMP was measured using small (<10 μm diam.) glass micropipettes connected to a servo-null system. We performed these measurements in the mid-wall of intact, Langendorff-perfused rabbit hearts with a balloon inserted into the left ventricular cavity. The balloon enabled us to stretch the cavity as well as to control cavity pressure during the interventions. We investigated how different ways of inducing tissue stretch (i.e., externally by increasing cavity pressure in intact heart or internally by distending the vasculature via changes in perfusion pressure) affected IMP—both in the passive state and during barium-induced contracture of the muscle.

2. Methods

2.1. Experimental preparations

New Zealand white rabbits of either sex were anesthetized with intravenous sodium pentobarbital, intubated, and ventilated with a mechanical ventilator. The heart was exposed via a midline sternotomy and arrested with direct injection of cold cardioplegic solution (composition in mmol/l: NaCl 114, KH₂PO₄ 0.4, MgSO₄ 1.0, NaHCO₃ 28.0, KCl 25.0, CaCl₂ 1.5, dextrose 5.6) into the aorta. The heart was immediately removed and perfused retrogradely via the aorta from a reservoir with room temperature, oxygenated, buffered solution having the same composition as the cardioplegic solution except with 3.5 mmol/l KCl. A schematic of the experimental setup is shown in Fig. 1. The perfusion pressure was measured from the side-port of a 3-way stopcock connected to the perfusion tubing using a fluid-filled transducer (P23dB, Gould, Inc., Hata Rey, Puerto Rico). The left atrium was removed and a pre-stretched balloon made from a finger cot was placed into the left ventricular cavity and secured by a pursestring suture around the mitral valve annulus. A plastic tube inserted into the balloon and connected to a 3-way stopcock allowed for instillation of saline and measurement of pressure in the balloon. It had been previously determined that the pressure in the balloon was negligible upon infusion of up to 3 cm³ volume. A short length of plastic tubing was introduced into the left ventricular cavity via a small cut in the apex to allow drainage of any fluid that accumulated between the walls of the ventricle and the balloon. The heart was then placed in a bath and secured so that the left ventricular free wall faced upwards. Holes were made in the right atrium and ventricle to allow the coronary effluent to drain into the specimen bath. A pump maintained the fluid level in the bath just below the upper surface of the left ventricular wall. The investigation conforms with the Guide for the Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Unsharpened glass micropipettes with inner diameters between 1 and 10 μm that had been prefilled with filtered and degassed 2 M NaCl were inserted into the left ventricular wall. The pipettes were inserted to a depth of about 2 mm which corresponded to a mark that had been previously drawn on the shank of the pipette. The micropipette...
was connected to a servo-null system (Model 5A, Instruments for Physiology and Medicine, San Diego, CA) which used a fluid-filled transducer (Gould, P23dB, Hata Rey, Puerto Rico) to measure the pressure at the tip. In preliminary studies we determined that changing the system gain with micropipette tips free in the fluid did not affect the output signal. When the tips were gently pushed against the surface of a rubber slab immersed under the fluid, however, changing the system gain produced a large deflection in the output signal. Similarly, when the micropipette was placed in a block of gelatin, which likely contained no free fluid, changing the system gain caused a large deflection in the output signal. Thus, during the protocols, to ensure that the tip of the micropipette was recording the pressure in a fluid space and not impinging against a solid surface after insertion, the position of the pipette was adjusted slightly with a micromanipulator until changing the system gain resulted in no change in the output signal.

2.2. Experimental protocols

With the heart in the passive state, the balloon was first opened to atmosphere to maintain zero pressure in the ventricular cavity. The reservoir connected to the perfusion cannula was raised or lowered stepwise so that the measured perfusion pressure was 50, 60, and 70 mmHg while IMP was recorded. The pipette was then removed and re-inserted at a nearby location and the entire procedure repeated. At least two such replicate measurements were made. Sufficient fluid was then introduced into the balloon to increase the LV pressure to about 30 mmHg, at which time IMP was again recorded at each of the 3 perfusion pressures, with replicates, as before. This portion of the protocol typically took less than 30 min to complete. The perfusate was then changed to a calcium-free one and allowed to perfuse for about 15 min. Then a steady-state contracture was induced by perfusing with the same solution as used for the passive studies except that 5 mmol/l barium replaced the calcium. After about 20–30 min when a steady contracted state had been achieved (as monitored by the balloon pressure at a constant volume), replicate measurements at the 3 perfusion pressures were repeated at the same balloon pressures as in the passive state.

The analog data consisting of IMP, balloon pressure, and perfusion pressure were digitized at a sampling rate of 10 Hz, recorded, and analyzed off-line on a minicomputer using custom software written in our laboratory for off-line analysis. The data reported here represent the steady-state average of each signal over about 5–10 s. Because of the garden-hose, or erectile, effect, there was a slight (a few mmHg) dependence of LV pressure on perfusion pressure. This effect, however, was small compared to the purposely large (30 mmHg) change in LV pressure that we induced by inflating the balloon (see Fig. 2). Therefore, we will ignore this effect and simply denote LV pressure as ‘low’ (P = 0 mmHg) or ‘high’ (P = 30 mmHg) for the balloon empty or inflated conditions, respectively.

2.3. Statistical analysis

We assessed the effects of perfusion pressure, LV pressure and contraction state on IMP by the non-parametric repeated measures ANOVA on ranks test using LV pressure (low versus high), contraction state (passive versus contracted) and perfusion pressure as trial factors. Multiple pairwise comparisons were made using the Student-Newman-Keuls test to assess the effect of the various trial factors. Statistical significance was assumed at the P = 0.05 level.

3. Results

Studies were performed in a total of 11 rabbit hearts. Fig. 2 shows representative recordings of the IMP in the passive state at 3 different perfusion pressures for low and high LV pressures. At both the low and high LV pressures there was a decrease in IMP with each decrease in perfusion pressure. At corresponding perfusion pressures the IMP was slightly greater at high than at low LV pressure.
Note the small change in LV pressure from its nominal value of 30 mmHg as perfusion pressure was changed (right panel). The results for several replicate measurements under all the experimental conditions for this same heart are summarized in Fig. 3. There was some variability among the replicates, but there was a clear dependence of IMP on perfusion pressure as well as a higher IMP in the contracted than in the passive state at each corresponding perfusion and LV pressure. For this heart at each perfusion pressure there was a slight increase in IMP when LV pressure was changed from 0 to 30 mmHg in the passive state but a decrease in the barium-contracted state (right panel). Fig. 4 illustrates the averages of the replicate measurements of IMP in all 11 hearts at a perfusion pressure of 50 mmHg at low and high LV pressures in both the passive and contracted states. Similar results were observed at perfusion pressures of 60 and 70 mmHg (data not shown).

Table 1 summarizes the results for all the hearts under all the conditions examined. Statistical analysis revealed significant \( P < 0.01 \) effects of perfusion pressure on IMP in both the passive and contracted states. In both the passive and contracted states as well as at both low and high LV pressures, there was a progressive and statistically significant \( P < 0.01 \) increase in IMP for each step in perfusion pressure. The magnitude of the perfusion pressure effect was significantly \( P < 0.01 \) greater in the contracted than in the passive state. At each perfusion pressure left ventricular pressure also significantly \( P < 0.01 \) affected IMP, but only in the passive and not in the contracted state.

### 4. Discussion

There are 3 major findings of this study: (1) at corresponding perfusion pressures, IMP was higher in the barium contracted than the passive state; (2) IMP was directly related to perfusion pressure with this effect being smaller in the passive than the contracted state; (3) at each perfusion pressure there was a small effect of LV cavity pressure on IMP in the passive but not the contracted state.

A unifying concept to explain these findings is that the pressure in an interstitial or any other fluid space surrounded by vessels and muscles represents the net resultant pressure.
of the solid stresses in the surrounding structures. Increasing stress by active contraction or passive stretching of any contiguous structure will increase IMP. Because the vessels and other tissues have differing stress–strain relationships, the net result of a particular intervention on IMP depends on how much and which structures are affected. For example, at a constant perfusion pressure in the passive state, stretching the wall increases IMP because the stresses in both vessels and myocardium are increased. Myocardial contraction increases tissue stiffness (and stresses) and, even with shortening or without stretching, is sufficient to increase IMP. Increasing perfusion pressure, on the other hand, distends rather than longitudinally stretches vessels, but this still increases their wall stresses sufficiently to increase IMP. In the contracted state this results in a larger increase in IMP than in the passive state because the surrounding myocardium is stiffer. Since the LV cavity, like the interstitial space, is surrounded by these solid constituents, the small increase in LV cavity pressure (the garden-hose effect) with increasing perfusion pressure (see, e.g., Fig. 2) is further evidence that this concept is correct. A recent model [14] using realistic non-linear ventricular and vessel elastic properties predicted the effects of perfusion pressure and lack of effect of LV cavity pressure on IMP that we observed experimentally. Under our experimental conditions the vessels are maximally dilated, so there is a direct relation between perfusion pressure and vessel distension (or coronary volume). Thus, one can view effects of perfusion pressure and vessel distention interchangeably—such would not be the case if vasomotor tone were intact, since volume (i.e., vessel stretch) could change independently of perfusion pressure.

These results support our contention that stretching the constituents of the LV wall but not cavity pressure *per se* is the major determinant of IMP. The effect of LV pressure in the passive state and lack of effect in the contracted state can be attributed to the differing stiffness of the wall in the two states. In the passive state, increasing LV pressure from 0 to 30 mmHg sufficiently stretches the wall to produce a small but significant increase in IMP at all 3 perfusion pressures. In contrast, in the much stiffer wall of the contracted state increasing LV pressure by the same amount results in so little stretch that there is no discernible change in IMP at any perfusion pressure. On the other hand, if LV cavity pressure itself were an important determinant of IMP, at a constant perfusion pressure one would have seen an increase in IMP with the balloon inflated in both passive and contracted states. A recent study provides further evidence that LV cavity pressure is not the primary determinant of IMP [12]. In both working and empty cat hearts subendocardial IMP, measured by micropipettes, was greater than LV cavity pressure. Despite likely differences in LV end-diastolic pressures, the diastolic IMP values were comparable in the working and empty hearts. Moreover, like our results, this study found a strong dependence of IMP on coronary perfusion pressure in both diastole and systole. The larger absolute values of IMP and the greater dependence on perfusion pressure could be due to the more limited time available for interstitial fluid movement in the short intervals between beats as compared to our contracture state.

Furthermore, even at the endocardial and epicardial surfaces—where many have made the argument that IMP should equal the LV pressure or atmospheric pressure, respectively (because this pressure is one of the boundary conditions)—one would not, in general, expect IMP and cavity pressure to be equal. Because there is a solid tissue interface between the cavity and the interstitial fluid space, according to Laplace’s law any curvature of the surface separating the two fluid compartments results in a pressure gradient between the compartments. Only in the unlikely case where there is either free communication of fluid between the cavity and interstitium and/or a completely flat solid surface separating them would one expect the IMP to equal either LV cavity or external pressure. Therefore, justifications of the validity of a particular method of measuring IMP based on arguments related to its relationship to LV cavity pressure or external pressure should be viewed with skepticism.

In summary, we found a direct relationship between perfusion pressure and IMP. When the LV cavity was passively stretched or the muscle contracted with barium, this relationship persisted. In the passive but not the contracted state, IMP increased with LV cavity pressure. These results can be explained by a unifying concept in which stretching of the structures surrounding the interstitial spaces—produced externally by increasing ventricular cavity size or internally by pressurizing vessels—but not LV cavity pressure *per se* is the major determinant of IMP. The specific effect of an intervention depends on the relative stiffness of and stresses in the surrounding structures.

**Appendix A. Limitations of the study**

An obvious limitation of any method that attempts to measure IMP is that the sensor unavoidably distorts the space into which it is placed. The larger the probe, the more distortion there is [7,15]. As discussed earlier, this distortion, because it affects the stresses of the surrounding vessels and myocardium, will affect IMP. Although we used the smallest practical micropipettes, these were still relatively large compared to the interstitial spaces in which the pressures were measured. Therefore, there is some degree of uncertainty associated with the absolute values of IMP. Since the variability of the replicate measurements was small, however, this uncertainty did not preclude being able to interpret relative or directional changes in the same preparation.
Another limitation is that we could not identify the exact location of the tip at the time the IMP was being measured. With unsharpened tips of this size, it is highly unlikely that the tip was in the cytoplasm of a cell and even more unlikely that it penetrated the wall of a vessel. Thus, we feel that the tips were likely measuring pressures in the interstitial space. Although we placed the pipettes at a nominal depth of 2 mm from the epicardial surface, some manipulation of the tip was required to ensure that the tip was free in a fluid space and not touching a solid surface. Furthermore, during muscle contracture with thickening of the wall, the position of the pipette relative to the epicardial and endocardial surfaces differed from that during the passive state. Because of these uncertainties, we did not attempt to assess the transmural distribution of IMP across the wall in either the passive or contracted state as has been done in many previous studies [2,8,9,11–13,16]. Since the gradients across the wall are probably not large in diastole [8,11], this limitation is not a big problem in the passive state. If, as many studies seem to indicate, there are large gradients of systolic IMP across the wall, our measurements in contracture might be somewhat confounded by being made at two different locations. The fact that replicate penetrations produced similar values, however, again suggests that this is not a severe problem.

Although a change in the stresses of the solid tissues is the mechanism whereby IMP (or the pressure in any fluid compartment in the heart) is affected, the resultant also depends on how each compartment is loaded. For example, it is well recognized that if the ventricular cavity remains isovolumic, the pressure in the cavity due to cardiac contraction will be much higher than if fluid leaves the cavity. The same principles should apply for the fluid pressure in the interstitial compartment [6,17]. Hence, the rather wide range of IMP values we observed in the different specimens may be related to different relative mobilities and leakiness of the interstitial fluid—both around the pipettes and among different interstitial compartments—in the specimens. Since leakage around the pipette tip is likely to be enhanced during muscle contraction when the tissue is stiffer, variable and uncontrolled amounts of leak from the compartment in which probes were located might also account for the wide range of reported IMP values during contraction [4,7,9,11,12,18].

Finally, the role of edema needs to be considered. Increasing fluid in the interstitial space stretches surrounding structures and increases IMP. In the presence of edema the effects of interventions such as stretching, contraction, etc. are going to be amplified compared with the situation with no edema. Perfusion with solutions like we used is well-known to cause edema 19, so this factor undoubtedly affected our results. Since we did not quantify the extent or the time course of edema formation in our hearts, an unknown portion of the IMP was due to edema. Our data suggested, however, that there was not a large time-dependent effect since the replicate measurements were separated by time yet clearly distinguished the effects of the various interventions. Moreover, at higher perfusion pressures more fluid should be transudated, so there might be additional effects to those of vessel distention already discussed. As shown in Fig. 2, however, after a change in perfusion pressure the responses appeared to be at steady state for much longer than the few seconds needed to record IMP. Thus, at least over this range of perfusion pressures, fluid transudation does not appear to play a significant role. Finally, it has been shown in perfused papillary muscles that a series of rapid cardiac contractions (3.3 Hz) squeezes fluid out of the interstitium and lowers IMP [20]. Since contracture is an even more sustained state than rapid pacing, edema was likely not a large factor during our barium contracture state.

References


