ABSTRACT

Left ventricular performance in the isolated dog heart was observed in a preparation in which left ventricular pressure and volume could be monitored continuously while the ventricle contracted isobarically by compressing air into a large chamber. By suddenly reducing the orifice connecting the ventricle to the chamber a constant load was imposed on the ventricle, abruptly forcing it to develop pressure in systole. This pressure increased over the ensuing 3 minutes while both the load and the end-diastolic pressure remained constant, implying that the sudden development of pressure by the ventricle was attended by a positive inotropic effect, otherwise known as homeometric autoregulation. Further studies showed this positive inotropic effect to be a function of the magnitude of the abrupt increase in systolic pressure and the time course of the experiment. β-adrenergic receptor blockade with propranolol decreased but did not abolish this effect. Infusion of norepinephrine did not enhance it. Increases in ventricular compliance that accompanied loading could not fully account for it. Evidence is presented that this positive inotropic effect may in part be mediated through the release of intrinsic catecholamines when the ventricle is forced to increase its systolic pressure.

ADDITIONAL KEY WORDS isolated heart homeometric autoregulation catecholamines norepinephrine ventricular compliance dialysis β-adrenergic receptor blockade dogs

The positive inotropic effect that accompanies an abrupt increase in the pressure developed by the ventricle has been appreciated for many years, having been noted by Anrep in 1912 and Patterson et al. in 1914 (1, 2). This effect may be described either as an increase in the strength of ventricular contrac-

From the Department of Pediatrics, Harvard Medical School, and the Cardiology Division of the Medical Service, Children's Hospital Medical Center, Boston, Massachusetts 02115.

This investigation was supported in part by U. S. Public Health Service Research Grant HE-10436 from the National Heart Institute and by N.I.H. Grant H-6144.

This work was performed during Dr. Monroe's tenureship of a Career Development Award from the National Institutes of Health.

Accepted for publication December 27, 1967.
ionic concentrations within the muscle cell; (3) an increase in the norepinephrine available to the muscle cell or an increase in the utilization of this hormone. Later work by Sarnoff et al. lent additional support to the second hypothesis (4). A subsequent publication from our laboratory gave evidence implicating the third (5). Recently, Sonnenblick et al. called attention to the increase in ventricular compliance observed to accompany an abrupt increase in the pressure developed by the ventricle (6). This was attributed to a viscous element within the myofibrils which, as implied by the authors, could relax under stress thereby lowering end-diastolic pressure in the face of a sustained increase in systolic pressure. Gilmore et al. likewise emphasized the importance of relating ventricular end-diastolic volume rather than pressure to ventricular performance in this phenomena and incidentally claimed that it was not observed in isolated cat papillary muscle (7).

To date, few of the workers referred to above have attempted to quantify this positive inotropic effect. Some have implied that the phenomenon may be accentuated by the infusion of norepinephrine (8). The same observers have shown it to persist despite the constancy of coronary flow (8). All in all, little data have been presented so far to elucidate other factors that either diminish or accentuate it.

Because the phenomenon is a delicate one, accurately described only under the most carefully controlled conditions, an attempt was made to study it in an isolated heart preparation that would allow precise monitoring of intraventricular pressure and volume. Although we have fallen short of our goal of attempting to pinpoint the precise

---

**Figure 1**

Schematic diagram of preparation. Oxygenated blood from donor enters from right (arrow) and is pumped to perfusion reservoir. Blood descends by gravity from a fixed height through filter, rotameter, and heat exchanger into right and left coronary arteries. Blood from coronary sinus leaves via right atrium, right ventricle, and pulmonary artery, and is pumped to return reservoir from which it returns to donor (arrow).
LEFT VENTRICULAR PERFORMANCE

mechanisms whereby the ventricle increases its contractility with increases in systolic pressure, certain characteristics of this phenomenon are noted as observed in an isolated heart preparation, and evidence for a contributory mechanism is presented.

Methods

The isolated heart preparation has been described previously in more detail and will be described only briefly below (9). Figures 1 and 2 are schematic diagrams of the preparation. Hearts from healthy mongrel dogs (18 to 25 kg) were excised under chloralose (60 mg/kg) and urethane (900 mg/kg) anesthesia. A grooved solid plastic button was ligated in the root of the aorta just below the ostia of the right and left coronary arteries. Cannulas were ligated in the aorta, pulmonary artery, and mitral orifice. The right atrium was closed with appropriate ligatures. The bundle of His was ligated so as to induce an atrioventricular block. The coronary circulation was then perfused by gravity with blood from an anesthetized donor; the blood first passed through a rotameter and a heat exchanger. Blood was returned under slight negative pressure from the pulmonary artery of the isolated heart to a reservoir and thence to the donor. The mitral cannula of the isolated heart was then attached to an enclosed Krogh spirometer through an arrangement of orifices and valves (Fig. 2); the heart was allowed to perform work by compressing air. End-diastolic pressure was determined by the pressure surrounding the spirometer and was transmitted to the ventricle through the J valve shown in the center of the figure. When the loading valve was open, the ventricle could contract isobarically by forcing its stroke volume of air through the large orifice of the loading valve into the 100-liter air chamber. Alternatively, when the loading valve was closed, the ventricle could develop pressure during systole by forcing air through the adjustable orifice seen on the left of the figure. With the described preparation, the ventricle could be allowed to contract isobarically at any desired end-diastolic pressure. Upon closing the loading valve, the ventricle abruptly developed a pressure in systole which could be predetermined by setting the adjustable orifice while end-diastolic pressure remained constant.

Heart rate was controlled by electrical stimulation of the distal portion of the ligated bundle of His with a pulse generator. Intraventricular pressure was monitored with a pressure transducer (Sanborn 267B). Absolute ventricular volume was monitored by the Krogh spirometer which was mechanically connected to a linear differential transducer (Sanborn 575 DT 250). A bipolar electrocardiogram was obtained through electrodes placed on opposite sides of the heart. Ventricular volume, intraventricular pressure, the electrocardiogram, and the mean systolic pressure of the donor were simultaneously recorded on a Sanborn Polyviso recorder (Sanborn 964).

In some of the studies an attempt was made to lower the concentration of circulating catecholamines in the perfusing blood. To accomplish this isolated lungs, in lieu of a donor dog, were used to oxygenate the blood perfusing the heart. In addition, the blood was dialyzed on its return from the heart by passing it through a dialysis unit (Travenol U210) as reported in a previous study (5). Catecholamine determinations were likewise made as previously described, using a modification of the trihydroxyindole method (5).

Results

1. VENTRICULAR PRESSURE-VOLUME RELATIONSHIPS FOLLOWING AN ABRUPT INCREASE IN SYSTOLIC PRESSURE

In all studies reported here, the ventricle was initially allowed to contract isobarically while the loading valve shown in Figure 2 remained open. Upon closing the loading valve,
the ventricle was abruptly forced to develop pressure as shown by the experiment illustrated in Figure 3. With the exceptions to be discussed, a gradual increase in the systolic pressure developed by the ventricle always followed the imposition of the load and end-diastolic pressure remained constant. The major portion of this increase occurred in the first 60 seconds following closure of the loading valve. Full development of the effect, however, usually required approximately 3 minutes except at very rapid heart rates, when less time was required.

Upon closing the loading valve, and thereby forcing the ventricle to develop pressure, there was a slight increase in end-diastolic volume

![Figure 3](image-url)

**Figure 3**

Tracing illustrates positive inotropic effect following abrupt development of pressure by ventricle. Top panel, intraventricular pressure. Bottom panel, intraventricular volume. Note gradual increase in ventricular systolic pressure reaching a plateau within 3 minutes while diastolic pressure remains constant. Paper speed, 1 mm/sec, with fast paper speed at far right, 25 mm/sec.

![Figure 4](image-url)

**Figure 4**

Tracing illustrating effect of returning end-diastolic volume to control volume after abruptly loading ventricle to develop pressure in systole. Top panel, intraventricular pressure. Bottom panel, intraventricular volume. Note very slight decrease in peak systolic pressure accompanying return of end-diastolic volume to control (vertical arrow). Further description in text.
and end-diastolic pressure remained constant. This increase was slight, as illustrated in Figures 3 and 4, varying from 1 to 2 ml. In general, this presumably viscous property of the ventricular wall lessened during the course of the experiment.

By carefully lowering the end-diastolic pressure, ventricular volume could be restored to its control (preload) volume after a sufficient period had elapsed for the ventricular pressure to stabilize following loading (lower panel, Fig. 4). When this was done, there was always a slight decrease in the systolic pressure of the ventricle, but hardly enough to reduce the ventricular pressure to that observed immediately after the load was imposed (upper panel, Fig. 4).

In five studies coronary flow was controlled either by a peristaltic pump or by varying the resistance of the perfusion system so that coronary flow did not change after the load was imposed. Despite such control of coronary flow, the positive inotropic effect that followed the abrupt development of ventricular pressure invariably appeared and was similar in magnitude.

2. FACTORS MODIFYING THE POSITIVE INOTROPIC EFFECT THAT FOLLOWS AN ABRUPT INCREASE IN SYSTOLIC PRESSURE

The positive inotropic effect following an abrupt increase in the pressure developed by the ventricle (Figs. 3 and 4) decreased with the passage of time in the described preparation. As shown in Figure 5, where the percent increase in systolic pressure following abrupt loading is measured repeatedly over several hours in one experiment, with zero time being the moment the isolated heart was first perfused, the percentage increase in this pressure declined steadily over 23 hours. In all studies this positive inotropic effect was greatest during the first hour and hardly perceptible 4 to 5 hours following the onset of perfusion.

Also, as shown in Figure 5, the percent increase in the pressure developed by the ventricle following the imposition of the load was directly related to the initial increase in pressure. In 20 preparations ventricles loaded to develop high pressures showed a greater positive inotropic effect, while in ventricles loaded to develop a relatively low pressure this effect was minimal ($P < .001$).

Heart rate was likewise a variable that appeared to modify the positive inotropic effect. As can be seen in Figure 6, which is a plot of the percent increase in systolic pressure following loading measured repeatedly over several hours in one experiment, this increase is, in general, more pronounced at...
faster heart rates. Figure 6 represents the average increase from 11 ventricles that were abruptly forced to develop the same systolic pressure. Here, despite the difference in the averages, it was difficult to establish a statistically significant difference in the described effect at the various heart rates observed. Inasmuch as the effect declined with the passage of time regardless of the heart rate, and a comparison of lines rather than points was necessary, it was felt advisable to resort to a ranking test in an attempt to establish a difference. By the Wilcoxon-Mann-Whitney test, one could not show a significant difference between the positive inotropic effect following abrupt loading at rates of 120 and 200 ($P > .05$) (10). In spite of this finding, it was nevertheless felt that if one were to compare this effect under two different circumstances, as in the ensuing studies, that heart rate should be similar under both circumstances to make the comparison valid.

In the studies previously described, the end-diastolic pressure of the ventricle was maintained at 15 mm Hg. The increase in ventricular performance following the abrupt imposition of a load was also observed at
higher and lower end-diastolic pressures. As, in general, the systolic pressure developed by the ventricle was a function of the end-diastolic pressure, and, furthermore, since the positive inotropic effect that followed abrupt loading was in turn a function of this systolic pressure, it was difficult to compare the positive inotropic effects at various end-diastolic pressures. For the sake of consistency, however, the performance of ventricles in all studies described here was compared at the same end-diastolic pressure.

Because the positive inotropic effect following abrupt loading could be influenced by heart rate, the initial pressure developed, time from perfusion, and possibly end-diastolic pressure it was advisable that these factors in the ensuing studies be comparable. Since this imposed limitations on subsequently described experiments, these factors were listed early in the presentation of results.

3. INFLUENCE OF PROPRANOLOL ON THE POSITIVE INOTROPIC EFFECT THAT FOLLOWS AN ABRUPT INCREASE IN SYSTOLIC PRESSURE

In 11 experiments the ventricles were allowed to contract isobarically at a pressure of 15 mm Hg and at a heart rate of 120 for 10 minutes and then abruptly loaded, as described in Methods, to develop 50 (± 1) mm Hg. As in previously described studies, the pressure developed by the ventricle increased asymptotically over a 3-minute period following the imposition of the load. Once the level of this pressure stabilized, the ventricle was allowed to contract isobarically for the ensuing 10 minutes at a different heart rate, after which the load was again imposed. This sequence was repeated at heart rates of 120, 140, and 200 for periods ranging from 2 to 4 hours. As seen in Figure 7, where the percent increase in systolic pressure that developed in the 3 minutes is measured repeatedly over several hours in one experiment, the positive inotropic effect following the abrupt imposition of a load diminished with time and showed considerable variability from ventricle to ventricle.

The behavior of six additional hearts was observed in the same manner at similar end-diastolic pressures, similar abruptly developed systolic pressures, and similar heart rates after the heart had been given an acute infusion of propranolol (0.25 to 4.0 mg/kg) just prior to perfusion. An additional slow infusion of propranolol was then instituted in order to maintain the effect of the drug (1/2 of the initial dose over a 40-minute period). The percent increase in systolic pressure that appeared in these hearts subsequent to the imposition of the load was likewise measured repeatedly over several hours in one experiment, as seen in Figure 7. There was, in general, less of a positive inotropic effect following the imposition of the load and a similar scatter in the results when compared with controls. In Figure 7, where the behavior of the ventricles was observed at a heart rate of 140, the difference in this effect between the control and blocked hearts was significant at the 0.05 probability level, using the referred ranking test (10). Statistically similar differences were also found at heart rates of 120 and 200. Despite the significance of the differences, complete suppression of the positive inotropic effect following imposition of the load could not be achieved even though the dose of propranolol was progressively increased to the extent shown.

4. INFLUENCE OF NOREPINEPHRINE ON THE POSITIVE INOTROPIC EFFECT THAT FOLLOWS AN ABRUPT INCREASE IN SYSTOLIC PRESSURE

Following the sudden imposition of the load in three hearts, ventricular performance was observed at a constant heart rate while the ventricle was so loaded as to develop an initial systolic pressure of 50 (± 1) mm Hg, and while coronary flow was controlled with a peristaltic pump. Following this control period, norepinephrine was infused into the blood perfusing the heart at such a rate as to induce a pronounced increase in the pressure developed by the ventricle. During the infusion of norepinephrine, the positive inotropic effect subsequent to abrupt loading was again observed at the same initial pressures while heart rate, end-diastolic pressure, and coronary flow were kept constant. In none of the three hearts could it be shown that the infusion of norepinephrine increased the positive inotropic effect that followed the imposition
of the load. In contradistinction to previous studies in which this effect could be reduced by prior infusion of propranolol, the infusion of norepinephrine failed to enhance it.

5. Positive Inotropic Effect Following an Abrupt Increase in Systolic Pressure during Perfusion of the Heart with Blood Low in Catecholamine

In five hearts the positive inotropic effect following an abrupt increase in systolic pressure was observed when a dialysis unit had been included in the perfusion circuit immediately after beginning to perfuse the heart. Under these circumstances, the perfusing blood was oxygenated by isolated lungs in lieu of a donor animal, as described in Methods. The dialysis unit served to remove epinephrine and norepinephrine from the perfusing blood, thereby reducing the concentration of epinephrine to undetectable levels and norepinephrine to below 0.7 μg/liter in the blood perfusing all five hearts so studied.

As in the study described in Section 3, the left ventricles of these hearts were abruptly loaded and unloaded over periods ranging from 2 to 4 hours, and the percent increase in systolic pressure that followed the imposition of the load was plotted as before (Fig. 8). When the behavior of these hearts was compared with that of hearts perfused with donor blood at comparable heart rates, end-diastolic pressure, and abruptly developed pressures, they showed a decrease in the positive inotropic effect that appeared subsequent to loading, as did the hearts with propranolol block. Figure 8 shows this comparison at a heart rate of 140 with a significant difference between the two groups at the 0.05 probability level (10). Significant differences of the same magnitude were found at heart rates of 120 and 200.

6. Relationship of the Positive Inotropic Effect Following an Abrupt Increase in Systolic Pressure to the General Performance Level of the Ventricle

In 17 of the previously described experiments, an attempt was made to relate the positive inotropic effect following abrupt loading to the general performance level of the ventricle, using normal hearts, those blocked with propranolol, and those perfused with blood low in catecholamines. In all 17 hearts the maximum pressure developed by each ventricle was noted at the beginning of the experiment at comparable heart rates and end-diastolic pressures when both the loading valve and adjustable orifice seen in
Figure 2 were closed and the ventricle thereby prevented from ejecting. In Figure 9 this maximum pressure, in turn, was plotted against the percent increase in systolic pressure following loading at a heart rate of 140, an end-diastolic pressure of 15 mm Hg, and at an abruptly developed systolic pressure of 50 mm Hg, likewise early in the experiment. From Figure 9 it is evident that there was considerable scatter in the attempted correlation. Here no definite relationship could be shown to exist between the positive inotropic effect following abrupt loading and the general performance level of the ventricle, either in the controls alone (dots) or in the combined normal ventricles, blocked ventricles, and ventricles perfused with catecholamine-free blood.

Discussion

In the described preparation a positive inotropic effect was noted following an abrupt increase in the pressure developed by the ventricle in accordance with previous reports (1-4, 7, 8). In addition, the preparation allowed observation and quantification of certain characteristics of this effect as summarized below.

(1) This positive inotropic effect appeared to be a function of heart rate (Fig. 6) although one could not prove this with convincing statistical significance. The effect was present despite the control of coronary flow; this is in keeping with a previous report (3). It should also be noted that this positive inotropic effect was a function of the abrupt increase in pressure as indicated in Figure 5; the greater the abrupt increase in pressure, the greater the positive inotropic effect. The fact that it was a function of the abrupt change in pressure bears relation to the findings of others and to possible mechanisms as subsequently discussed.

(2) This positive inotropic effect decreased during the course of the experiment. This, too, is stressed as it indicates a complicating factor when comparisons were attempted and when the effect was observed at different points in time. As the preparation normally does not deteriorate during the period observed, one could not attribute the decrease in the effect to deterioration of the preparation (11). This decrease, however, raises the possibility that the effect may be due, at least in part, to a substance that diminishes with time in the preparation used.

(3) In the studies described there appeared to be a small increase in diastolic ventricular volume following the abrupt imposition of the load while end-diastolic pressure remained constant (Fig. 4). This increase in ventricular compliance has been observed by others and attributed to a series viscous element within the muscle which is stretched when systolic pressure is elevated, despite the fact that end-diastolic pressure remains the same (6, 7).

Although such stretching of the viscous element should not in theory further stretch the contractile element, one should remember that ultrastructural knowledge of the precise location of either of these elements is lacking and that the two could indeed be firmly tied together, or, for that matter, the contractile element itself could be viscous. Furthermore, there is also the possibility, however small, that the increase in end-diastolic volume at a constant end-diastolic pressure would tend...
to increase the tension on the contractile element in the face of the Laplace relationship and invoke a positive inotropic effect through Starling's law.

In the results presented, however, one could only account for very little of the positive inotropic effect that accompanied the abrupt imposition of a load to the increase in diastolic compliance discussed above. As illustrated in Figure 4, when diastolic volume was restored to the control volume following this positive inotropic effect (lower panel), there was a very slight accompanying decrease in ventricular performance (upper panel), amounting to only 20% of the over-all positive inotropic effect. To this extent it may be that an increased diastolic compliance could account, in part, for the positive inotropic effect observed. In the reported data, however, this part was small, bordering on the limits of measurement.

(4) The magnitude of the positive inotropic effect described was, in part, dependent on the prevailing catecholamine state to the extent shown by infusion of norepinephrine, by perfusion with blood low in catecholamines, or by β-adrenergic receptor blockade. Those experiments in which this effect was not enhanced by the infusion of norepinephrine may at first appear to be at variance with the studies of others who noted the opposite (8). However, in this report the effect of norepinephrine was observed when the abrupt increase in pressure was maintained the same as the control value. Because the greater the abrupt increase in pressure, the greater its accompanying positive inotropic effect (Fig. 5), and because norepinephrine was administered at a rate sufficient to increase the contractility of the heart, one would have doubtless observed an increase in this positive inotropic effect with an infusion of norepinephrine had not the level of the abrupt increase in pressure been controlled.

In those studies in which hearts were perfused with dialyzed blood and the catecholamine levels were very low, there was a significant decrease in the positive inotropic effect that accompanied loading. Here it should be noted that the performance of these ventricles, as indicated by their peak systolic pressure, was not significantly different from the controls (Fig. 9). The authors are aware that, by dialysis, any number of compounds of small molecular size could have been removed from the perfusing blood, compounds that could indeed be involved in the mechanism of the phenomenon under discussion. As catecholamines and presumably their precursors were found to be reduced in these studies, at least the suspicion of their implication is warranted although their actual implication is far from proved.

At first glance, there may seem to be an inherent contradiction in the evidence that an increased concentration of norepinephrine could not be shown to increase the positive inotropic effect that accompanies abrupt loading, whereas with a lowering of plasma catecholamines, this effect is decreased. One should be careful in interpretation here, as it could well be that catecholamines, even at low plasma levels, enhance the effect, that the effect increases only to a critical plasma concentration, and that any further increase beyond this concentration accomplishes little.

Further suspicion of the implication of catecholamines is based on those studies in which the positive inotropic effect that accompanies abrupt loading was reduced after prior treatment of the heart with propranolol. It should be emphasized that as in the studies described earlier the abrupt change in pressure was similar to that of controls. Here again, however, the implication of catecholamines in the described phenomenon is not fully proved. Evidence that propranolol depresses ventricular performance has been noted in the past and was indeed noted in our experiments as shown in Figure 9 (12). One could argue, therefore, that a factor inseparably tied with ventricular performance is responsible for the effect observed. Evidence against this inseparability, however, is presented by those studies in which the positive inotropic effect that accompanies abrupt loading was reduced in the presence...
of low catecholamine concentrations but ventricular performance was comparable to that of controls (Fig. 9). Furthermore, if one compares Figure 7 with Figure 9, it is evident that the over-all reduction of the effect in blocked hearts is greater than the reduction in performance.

This report is consistent with previous studies showing a positive relationship between the pressure developed by the ventricle and the rate of norepinephrine release in which it was suggested that norepinephrine played a part in the positive inotropic effect that accompanies abrupt loading in both denervated and non-denervated hearts (5, 13). Since in the present study this positive inotropic effect could be significantly reduced by prior treatment of the heart with propranolol, more evidence is presented supporting the hypothesis that the additional increment of norepinephrine released by the heart, when the ventricle is forced to increase its systolic pressure, may, in part, serve to cause this effect.

The authors are in agreement with the views of others who postulate that multiple mechanisms may well be involved in the positive inotropic effect that accompanies abrupt loading (3, 6, 7). To that end, it is hoped that the preparations used in this study and the data derived from it (showing the extent to which the effect may or may not be modified by such factors as coronary flow, heart rate, time, level of the abrupt increase in pressure, ventricular volume, catecholamines, and propranolol) will be of use in separating the mechanisms involved. Previous reports have tended to dismiss the involvement of catecholamines in a hypothetical mechanism, presumably because the phenomenon has been noted in reserpinized preparations (7, 14). We have likewise noted the effect in hearts pretreated with reserpine and do not believe that a single mechanism involving catecholamines can fully account for the phenomenon. To the extent, however, that the effect was found to be diminished in controlled, blocked hearts, it is felt that a contributory mechanism involving catecholamines should seriously be considered.

Acknowledgments
The authors are indebted for the technical assistance of Philip E. Waithe and Victoria S. Moore, and to Ayerst Laboratories for supplying the propranolol.

References
12. Levy, J. V., and Richards, V.: Inotropic and chronotropic effects of a series of β-adrenerg-
344 MONROE, LA FARGE, GAMBLE, ROSENTHAL, HONDA


Left Ventricular Pressure-Volume Relations and Performance as Affected by Sudden Increases in Developed Pressure

R. G. MONROE, C. G. LA FARGE, W. J. GAMBLE, A. ROSENTHAL and S. HONDA

Circ Res. 1968;22:333-344
doi: 10.1161/01.RES.22.3.333

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/22/3/333

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/