Effect of Norepinephrine and Cyclic AMP on Intracellular Sodium Ion Activity and Contractile Force in Canine Cardiac Purkinje Fibers

Mark S. Pecker, Wook-Bin Im, Jong K. Sonn, and Chin O. Lee

The effect of norepinephrine on the Na\(^+\)-K\(^+\) pump was investigated by simultaneously measuring intracellular sodium ion activity (\(a_{\text{Na}}\)) and contractile force of canine cardiac Purkinje fibers driven at 1.0 Hz in K\(^+\)-free solution, high K\(^+\) solution, and in the presence of tetrodotoxin. In Tyrode solution containing 5.4 mM [K\(^+\)], 10\(^{-4}\) M norepinephrine decreased \(a_{\text{Na}}\), whereas in K\(^+\)-free solution 10\(^{-4}\) M norepinephrine did not lower \(a_{\text{Na}}\). 16.2 mM [K\(^+\)], decreased \(a_{\text{Na}}\) from 8.8 ± 0.9 mM to 6.5 ± 0.5 mM (mean ± SD, \(n = 5\)). Exposure to 10\(^{-4}\) M norepinephrine in the presence of high [K\(^+\)], further decreased \(a_{\text{Na}}\) by 0.7 ± 0.4 mM. This further decrease was prevented by exposure to 2.5 \(\times 10^{-4}\) M strophanthidin (\(n = 4\)). Blockade of the fast sodium channel with 5 \(\times 10^{-4}\) M tetrodotoxin lowered \(a_{\text{Na}}\) from 8.5 ± 1.3 mM to 7.4 ± 1.1 mM (\(n = 4\)). Exposure to 10\(^{-4}\) M norepinephrine in the presence of tetrodotoxin further lowered \(a_{\text{Na}}\) by 0.9 ± 0.2 mM. We also studied the effects of the analogues of adenosine 3'5'-cyclic monophosphate, N6, 2'-O-dibutyryladenosine 3'5'-cyclic monophosphate, and 8-(4-chlorophenylthiol)-adenosine 3'5'-cyclic monophosphate on \(a_{\text{Na}}\) and twitch tension. Both analogues lowered to \(a_{\text{Na}}\) and increased twitch tension mimicking the effects of norepinephrine. Our results support the hypothesis that norepinephrine lowers \(a_{\text{Na}}\), by stimulating the Na\(^+\)-K\(^+\) pump in this tissue. This stimulation appears to be mediated by adenosine 3'5'-cyclic monophosphate and does not appear to be due to intercellular K\(^+\) accumulation. The results also are consistent with the hypothesis that lowering \(a_{\text{Na}}\) by norepinephrine or cyclic AMP plays a role in the control of contractile force in cardiac Purkinje fibers. (Circulation Research 1986;59:390-397)
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Materials and Methods

Mongrel dogs of either sex weighing 8–12 kg were anesthetized by intravenous administration of sodium pentobarbital (30 mg/kg). The heart was quickly excised through an intercostal incision and transferred to oxygenated Tyrode solution at room temperature. Free running bundles of Purkinje fibers of 0.5–1.0 mm diameter and 5–12 mm length were dissected from both ventricles. A fiber bundle was mounted in a narrow channel of a muscle chamber, with one end fixed to the Sylgard floor of the chamber and the other end connected to a tension transducer (Model 405, Cambridge Technology, Cambridge, Mass.) by means of a silver wire 25 μ in diameter. Oxygenated Tyrode solution was perfused through the channel at a constant rate so that solution changes around the tissue took place in several seconds. Normal Tyrode solution contained (in mM) 137 NaCl, 5.4 KCl, 1.8 CaCl₂, 1.05 MgCl₂, 11.9 NaHCO₃, 0.45 NaH₂PO₄, and 5.0 dextrose. High K (16.2 mM) Tyrode solution was made by replacing 10.8 mM NaCl with KCl in the normal Tyrode solution. K-free Tyrode solution was made by omitting the KCl without other changes in the normal Tyrode solution. The bath temperature was 36–37°C. Solutions were gassed with a mixture of 97% O₂ and 3% CO₂ and the pH of all solutions were 7.3–7.4. The Purkinje fibers were continuously driven at 1.0 Hz throughout the experiments by stimulating electrodes connected to a stimulus isolation unit (Model 305T; W-P Instruments, New Haven, Conn.) through a stimulator (Model 301T; W-P Instruments, New Haven, Conn.) by means of a silver wire 25 μ in diameter. Oxygenated Tyrode solution was perfused through the channel at a constant rate so that solution changes around the tissue took place.

One milligram of Tetrodotoxin (Sankyo Co., Ltd., obtained through Calbiochem-Behring Corp., LaJolla, Calif.) was dissolved in 2 ml of deionized water, and this stock solution was kept refrigerated. A stock solution of norepinephrine (Levophed Bitartrate, Breon Laboratories, New York, N.Y.) was prepared at the time of the experiment and kept refrigerated and in the dark until diluted just prior to use. A stock solution of DBcAMP and 8-(4-chlorophenylthio)-adenosine 5′-cyclic monophosphate (8-ClPheScAMP) (Sigma Chemical Co., St. Louis, Mo.) were dissolved in Tyrode solution immediately prior to use. A stock solution of 10−3 M strophanthidin (Sigma Chemical Co., St. Louis, Mo.) in deionized water was prepared and, prior to use, diluted with the appropriate solution.

Intracellular Na ion activity (aNa) was measured with Na⁺-selective microelectrodes made with the neutral carrier ETH 227. The Na⁺-selective electrodes were calibrated before and after each experiment. The Purkinje fibers were impaled with both conventional and Na⁺-selective microelectrodes. The distance between the impalements was less than 1 mm. aNa of canine cardiac Purkinje fibers stimulated at a constant rate of 1.0 Hz was determined as described previously. In order to measure aNa continuously in electrically driven fibers we used two identical low-pass filters (with a fixed frequency of 0.24 Hz) to remove the fluctuations in transmembrane potential recorded by conventional and Na⁺-selective microelectrodes. In the text, Vm refers to the filtered transmembrane potential.

All results are expressed as mean ± standard deviation. Changes of aNa within each intervention were analyzed by paired t test. Correlations were determined by linear regression. Comparisons between different experiments were analyzed by analysis of variance with pairwise t tests using the Bonferroni adjustment for multiple comparisons. All analyses were performed using the BMDP statistical software package.

Results

Effects of Norepinephrine in the Presence of Different K Concentrations

Figure 1 shows the effect of 10−6 M norepinephrine on filtered membrane potential (Vm), aNa, twitch tension (T) and action potential in a canine cardiac Purkinje fiber bathed in normal Tyrode solution. This experiment shows results that are similar to those reported previously. It demonstrates the effects of norepinephrine in this preparation. On exposure to 10−6 M norepinephrine twitch tension rapidly increases to a peak level and then decreases (Figure 1C) whereas aNa,

![Figure 1](http://circres.ahajournals.org/doi/figure/10.1161/01.RES.89.4.391)

**FIGURE 1.** Effect of norepinephrine on filtered membrane potential (Vm), aNa, twitch tension (T) and action potential in a canine cardiac Purkinje fiber bathed in normal Tyrode solution. On exposure to 10−6 M norepinephrine twitch tension rapidly increases to a peak level and then decreases (Figure 1C) whereas aNa,
new norepinephrine increases twitch tension and then recover to preexposure values in normal Tyrode solution. Figure 4 shows that K-free solution increased some tension but had little effect on twitch tension. During exposure to norepinephrine, twitch tension was decreased by blocking the fast sodium channel with tetrodotoxin (TTX). Addition of 5 × 10−6 M TTX decreased twitch tension and action potential duration as shown in traces B and C respectively. The filtered membrane potential during cessation of contraction during exposure to 16.2 mM [K+]o decreases (Figure 1B). Continuous exposure to norepinephrine maintains twitch tension at a level lower than the control tension. Reexposure to normal Tyrode solution produces a rapid decrease in twitch tension. During recovery from norepinephrine the action potential duration shortened and the maximum decrease of a^, averaged 1.3 ± 0.4 mM to a level of 5.9 ± 0.2 mM (p < 0.02).

In order to ascertain that the fall in a^, during exposure to high K Tyrode solution was due to pump stimulation, we tested the effect of norepinephrine in the presence of K-free bathing solution. Figure 4 shows that K-free solution increased action potential duration by 0.7 ± 0.4 ms and then in 16.2 mM [K+]o and 2.5 × 10−6 M strophanthidin. This concentration of strophanthidin increased a^, and also prevented norepinephrine from lowering a^, just as it does in the setting of normal Tyrode solution. Similar results were obtained in 6 experiments in 4 different tissues.

Effects of Norepinephrine on a^, in the Presence of Tetrodotoxin

Figure 5 shows the effect of norepinephrine when a^, was lowered by blocking the fast sodium channel with tetrodotoxin (TTX). Addition of 5 × 10−6 M TTX decreased twitch tension and action potential duration as shown in traces B and C respectively. The filtered membrane potential decreases (Figure 1B). Continuous exposure to norepinephrine maintains twitch tension at a level lower than the control tension. Reexposure to normal Tyrode solution produces a rapid decrease in twitch tension. During recovery from norepinephrine the action potential duration shortened and the maximum decrease of a^, averaged 1.3 ± 0.4 mM to a level of 5.9 ± 0.2 mM (p < 0.02).

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FIGURE 4. Effect of norepinephrine in the presence of K-free bathing solution on the $V_m$, $\Delta V_m$, and tension. Panel A: Filtered membrane potential during contraction and the resting membrane potential during cessation of contraction during exposure to K+-free solution. Panels B and C: $\Delta V_m$ and tension recordings, respectively. Note a transient dislodgement of Na+-selective microelectrode (trace B). Norepinephrine did not decrease $\Delta V_m$ in K-free solution. See text for further explanation.

(V$_m$) hyperpolarized as shown in trace A. The hyperpolarization in $V_m$ was largely due to a shortening of the action potential and to a more negative plateau (action potential "b" in Figure 5D). Addition of norepinephrine in the presence of TTX caused a further fall in $\Delta V_m$. Although norepinephrine in the presence of TTX increased twitch tension, the tension increased to a level that was lower than the control tension in Tyrode solution. This is consistent with the idea that lowering $\Delta V_m$ plays a role in the control of contractile tension through a Na+-Ca2+ exchange. Washout of norepinephrine led to recovery of $\Delta V_m$ to the level it had been lowered to by TTX. In the presence of TTX, norepinephrine shifted the action potential plateau to a more positive level (action potential "c" in Figure 5D), although $V_m$ only depolarized slightly. In the absence of TTX, $V_m$ slightly hyperpolarized on the exposure to norepinephrine. In both cases, however, $\Delta V_m$ decreased and $V_m$ changes might not have played a significant role in the $\Delta V_m$ change. After washout of TTX, $\Delta V_m$ recovered to the control level in Tyrode solution. In 4 experiments in 4 tissues; control $\Delta V_m$ averaged 8.5 ± 1.3 mM and 5 × 10^{-6} M TTX lowered $\Delta V_m$ to a mean of 7.4 ± 1.1 mM ($p<0.05$). Exposure to 10^{-6} M norepinephrine in the presence of TTX further lowered $\Delta V_m$ by 0.9 ± 0.2 mM to 6.5 ± 1.0 mM ($p<0.005$).

The Effect of Analogues of cAMP on $\Delta V_m$ and Twitch Tension

In cardiac Purkinje fibers the effect of norepinephrine on $\Delta V_m$ is presumably mediated by β receptors since propranolol blocks the response and isoproterenol mimics it. If so, this response should be mediated by cAMP. We therefore tested the effects of two analogues of cAMP, 8-ClPheScAMP and DBcAMP, on $\Delta V_m$ and twitch tension. These analogues were used because they are more stable than cAMP itself.

Figure 6 shows the effect of 10^{-6} M 8-ClPheScAMP on $V_m$, $\Delta V_m$, twitch tension (T) and action potential in a canine cardiac Purkinje fiber. As shown in Figure 6A, 8-ClPheScAMP caused a hyperpolarization of $V_m$. This was due to a combination of elevation of the plateau and shortening of the action potential, with slight hyperpolarization in diastolic membrane potential (Figure 6D). These effects on the action potential are similar to those of norepinephrine (see Figure 1D).
After a delay of 3–4 minutes, twitch tension rose gradually. In this experiment no change in diastolic tension occurred; in some experiments a fall in diastolic tension was present during the increase in twitch tension. During the recovery, twitch tension fell to values below control (undershoot) (Point c in Figure 6C and twitch tension “c” in 6D). At that point, the plateau of the action potential was similar to control levels, but the action potential duration was still somewhat shortened (action potential “c” in Figure 6D). $a_{in}$ fell slowly after a delay and recovered gradually in concert with the recovery from the undershoot of tension. Note that during the undershoot of tension, $a_{in}$ was lower than the control $a_{in}$ prior to the exposure to 8-ClPheScAMP. Thus, the undershoot of tension appears to be related to the low $a_{in}$. In 25 tests in 7 tissues, exposure to $10^{-4}$ M 8-ClPheScAMP for 5–10 minutes increased twitch tension by 100 ± 63%, and the largest decrease from control twitch tension during the undershoot averaged $-28 \pm 8%$. $a_{in}$ was measured in 18 of these tests (6 tissues) and averaged 8.4 ± 2.7 mM under control conditions. $a_{in}$ fell by an average of $1.0 \pm 0.4$ mM to a value of 7.4 ± 2.5 mM during exposure to 8-ClPheScAMP ($p < 0.00005$).

Exposure of fibers to 2–5 mM DBcAMP for 6–10 minutes produced changes similar to those produced by 8-ClPheScAMP, although with a slightly longer time course. In 16 tests in 7 tissues the maximum increase in twitch tension was $94 \pm 67\%$, and the maximum decrease in twitch tension during the undershoot was $-23 \pm 8\%$. $a_{in}$ was measured in 11 of these tests and averaged 7.1 ± 1.3 mM under control conditions and $a_{in}$ declined by $0.9 \pm 0.3$ mM to an average minimum value of $6.2 \pm 1.2$ mM ($p < 0.00005$).

These results are qualitatively similar to those obtained with norepinephrine except that the time course of onset and recovery of the effect was slower with the cAMP analogues. In particular, the increase in twitch tension was slower to develop. We did not define a level of maximum tension (see Figure 6C), and so it is not clear if tension would have declined from a peak as it does during exposure to norepinephrine.

**Discussion**

This study is concerned with three major questions: 1) Is the decrease of $a_{in}$ in the presence of norepinephrine due to stimulation of the Na⁺-K⁺ pump or is it caused by other factors such as K⁺ accumulation in the intercellular space or a decrease in Na⁺ influx? 2) Does cAMP mimic the effect of norepinephrine on $a_{in}$? 3) Does the fall in $a_{in}$ in the presence of norepinephrine play a role in the control of contractile force in cardiac Purkinje fibers? The results indicate that 1) the decrease in $a_{in}$ is due to stimulation of the Na⁺-K⁺ pump by norepinephrine independent of K⁺ accumulation in the intercellular space. A decrease in Na⁺ influx, although difficult to dissect out, seems to play at most a minor role. 2) Stimulation of the Na⁺-K⁺ pump by norepinephrine is mediated through cAMP, and 3) the changes in tension during washout are consistent with a role for the decrease in $a_{in}$ in the control of contractile force, presumably via Na⁺-Ca²⁺ exchange.

**Norepinephrine and the Na⁺-K⁺ Pump**

One purpose of these studies was to evaluate whether pump stimulation in the presence of catecholamines might be due to potassium accumulation in the intercellular space due to an increase in potassium conductance. Canine cardiac Purkinje fibers were chosen for study since their intercellular spaces are relatively less constrained in the dog than in other species. Removal of potassium from the external solution substantially inhibits the sodium pump in cardiac tissue. If norepinephrine caused sufficient potassium leak to elevate potassium in the intercellular space, stimulation of the sodium pump, and a fall in $a_{in}$, or at
least in the rate of rise of a\textsubscript{Na}, would be expected. In our studies exposure to norepinephrine did not observably affect a\textsubscript{Na} in fibers bathed in K-free solution (Figure 4). This negative result, which is similar to that reported on the effect of norepinephrine in the presence of cardiotonic steroids,\textsuperscript{7} is consistent with an effect of norepinephrine on the sodium pump, independent of potassium accumulation. However, in the presence of K-free solution, Purkinje fibers depolarize to a level of about -30 mV (see Figure 2A), membrane resistance increases and K\textsuperscript{+} conductance falls.\textsuperscript{22,23} Therefore, in K-free solution, norepinephrine might not increase K\textsuperscript{+} conductance as it does in the presence of normal [K\textsuperscript{+}]. although it does hyperpolarize the membrane potential (see Figure 4A).

We therefore examined the effects of norepinephrine in the presence of 16.2 mM [K\textsuperscript{+}]. This concentration causes near maximal pump stimulation achievable from elevating [K\textsuperscript{+}].\textsuperscript{20,21} Exposure to 16.2 mM [K\textsuperscript{+}] depolarizes the fiber and decreases a\textsubscript{Na} from control levels. This decrease probably results from a decrease in sodium influx in the presence of action potentials, and perhaps due to effects of depolarization per se on sodium flux.\textsuperscript{24} A change in pump activity is unlikely to be an important contributor to this decrease since a\textsubscript{Na} doesn’t change in voltage-clamped fibers when [K\textsuperscript{+}] is raised from 5.4 to 15 mM.\textsuperscript{27} In the setting of high [K\textsuperscript{+}], norepinephrine caused a further decline in a\textsubscript{Na} (Figure 2). Further, the norepinephrine-induced decrease in a\textsubscript{Na} in the setting of 16.2 mM [K\textsuperscript{+}], is blocked by strophanthidin (Figure 3), just as it is in the presence of 5.4 mM [K\textsuperscript{+}].\textsuperscript{7} These results strongly indicate that norepinephrine stimulates the sodium pump independently of an increase in K\textsuperscript{+} conductance since any potassium accumulation could not be expected to enhance sodium pump activity significantly beyond that caused by 16.2 mM [K\textsuperscript{+}] in the presence of 16.2 mM [K\textsuperscript{+}].

A strong linear correlation is present between the absolute change in a\textsubscript{Na} after norepinephrine and the prenorepinephrine a\textsubscript{Na} for all 14 exposures in normal Tyrode, high [K\textsuperscript{+}], and TTX (r = 0.73, p < 0.001), and this is supported by the trends present among the three groups (see Table 1). Such a correlation is compatible with the pump-leak model, assuming first-order dependence of sodium efflux on a\textsubscript{Na}, as has been found empirically at levels of a\textsubscript{Na} in the range of these experiments.\textsuperscript{21,28,29} If norepinephrine changes the rate exchange of Na\textsuperscript{+} efflux similarly in each experimental condition without affecting influx, then in the steady state:

\[ k \cdot (a_{Na}) = k_{Ne} \cdot (a_{Na,Ne}) \text{ or } k_{Ne}/k = (a_{Na})/(a_{Na,Ne}) \]

where k and k\textsubscript{Ne} are the rate constants of Na\textsuperscript{+} efflux in the absence and presence of norepinephrine, respectively, and a\textsubscript{Na} and a\textsubscript{Na,Ne} are the steady-state intracellular sodium ion activities before and during exposure to norepinephrine, respectively. This model predicts that the absolute change in a\textsubscript{Na} after norepinephrine should be proportional to the prenorepinephrine a\textsubscript{Na} while the percent decrease and the ratio a\textsubscript{Na}/a\textsubscript{Na,Ne} should be constants, with this ratio indicating the degree of pump stimulation. The ratios for each experimental group are shown in Table 1 and are not significantly different (p > 0.10 for each comparison). Further, the percent decrease in a\textsubscript{Na} after norepinephrine for the three groups are not significant (p > 0.10 for each comparison). However, contrary to the model, the absolute decrease in a\textsubscript{Na} with norepinephrine is not significantly different among the three groups (p > 0.10 for each comparison), although the trend is stronger than for the ratio or percent decrease. Thus, our data are compatible with the simplest model for the norepinephrine effect on a\textsubscript{Na}, a single effect on the pump (here with 10–20% stimulation by norepinephrine). Reasons for departures from the model could include scatter of the control a\textsubscript{Na} levels, different degrees of pump stimulation under the different experimental circumstances or an effect on sodium influx.

**Effect of Norepinephrine on Na\textsuperscript{+} Influx**

It is possible that part of the effect of norepinephrine to lower a\textsubscript{Na} derives from alterations in Na\textsuperscript{+} influx. In our experiments, TTX did not block this effect, suggesting that the fast sodium channel is not principally involved. Further, the prevention of the effect by strophanthidin in normal Tyrode’s solution,\textsuperscript{7} 16.2 mM Tyrode’s solution (Figure 2), and in the presence of TTX\textsuperscript{10} as well as by K-free solution (Figure 4) argue against a role for alterations of Na\textsuperscript{+} influx under a variety of membrane and contractile conditions.

### Table 1. Ratio of a\textsubscript{Na} Before Norepinephrine or Analogues of cAMP to a\textsubscript{Na} During Norepinephrine Exposure (a\textsubscript{Na,Ne}).

<table>
<thead>
<tr>
<th>Bathing solution</th>
<th>a\textsubscript{Na} (mM)</th>
<th>a\textsubscript{Na,Ne} (mM)</th>
<th>a\textsubscript{Na}/a\textsubscript{Na,Ne}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyrode</td>
<td>8.0 ± 0.4</td>
<td>6.8 ± 0.4</td>
<td>1.19 ± 0.06</td>
</tr>
<tr>
<td>16.2 mM K Tyrode</td>
<td>6.5 ± 0.5*</td>
<td>5.9 ± 0.2</td>
<td>1.11 ± 0.06</td>
</tr>
<tr>
<td>Tyrode plus TTX</td>
<td>7.4 ± 1.1</td>
<td>6.5 ± 1.0</td>
<td>1.15 ± 0.03</td>
</tr>
<tr>
<td>Tyrode</td>
<td>8.4 ± 2.7</td>
<td>7.4 ± 2.5</td>
<td>1.15 ± 0.08</td>
</tr>
<tr>
<td>Tyrode plus TTX</td>
<td>7.1 ± 1.3</td>
<td>6.2 ± 1.2</td>
<td>1.15 ± 0.06</td>
</tr>
</tbody>
</table>

*All data are expressed as mean ± SD. Number of experiments are indicated in text.*

*p < 0.01 in comparison with a\textsubscript{Na} in Tyrode solution.
finding that apparent pump stimulation by norepinephrine ($a^+_{\text{Na}}/a^+_{\text{Na},\text{Na}}$) is similar under different conditions is also in keeping with this hypothesis. Thus, although norepinephrine may have direct or indirect effects on Na$^+$ influx, they do not play a major part in the observed changes in $a^+_{\text{Na}}$.

**Analogues of cAMP and the Na$^+-K^+$ Pump**

Our results with 8-ClPheScAMP and 2-ClPheScAMP show that these agents mimic the effects of norepinephrine in several important aspects. First, analogues of cAMP cause both positive and negative inotropic effects. The positive inotropic effects occur more slowly than those due to norepinephrine. The negative inotropic effects are unmasked during washout of the agent. Second, both norepinephrine and the cAMP analogues affect the action potential in a similar way — elevating the plateau and shortening the duration. Despite substantial shortening of action potential duration during norepinephrine and 8-ClPheScAMP exposure, twitch tension increased to more than twice control levels (Figures 1 and 6). During the undershoot of twitch tension, action potential duration was slightly shortened compared to control. It is not clear how the changes in action potential duration contributed to the changes in tension. Third, both agents lower $a^+_{\text{Ca}}$, and the recovery of $a^+_{\text{Ca}}$ parallels the recovery of twitch tension from the undershoot (Figure 1B, C and 6B, C). Further, the degree of pump stimulation as judged by the undershoot (Figure IB, C and 6B, C). The present results indicate that it is likely that both of these effects are mediated by cAMP.

*Note added in proof:* Two recent reports bear on this work. Desilets and Baumgarten (Am J Physiol 1986; 251:H218–H225) found that isoproterenol lowered $a^+_{\text{Ca}}$ and stimulated the Na$^+$–K$^+$ pump in isolated rabbit cardiac myocytes, independently of possible K$^+$ accumulation outside the cell. A kinetic analysis of their data led them to conclude that isoproterenol also augmented passive Na$^+$ influx. Glitsch and Rasch (Pflüger's Arch 1986;406: 144–150) found that catecholamines increased $a^+_{\text{Ca}}$ in sheep cardiac Purkinje fibers, in contradiction to previous work in dog and rabbit. They also conclude that catecholamines augment passive Na$^+$ influx.

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