Decreased cardiac output at the onset of diabetes: renal mechanisms and peripheral vasoconstriction

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Brands, Michael W., Sharyn M. Fitzgerald, William H. Hewitt, and Allison E. Hailman. Decreased cardiac output at the onset of diabetes: renal mechanisms and peripheral vasoconstriction. Am J Physiol Endocrinol Metab 278: E917–E924, 2000.—Recently we reported that hindquarter blood flow, measured 24 h/day, decreased progressively over the first 6 days of type 1 diabetes in rats. That response, coupled with the tendency of mean arterial pressure to increase, suggested a vasoconstrictor response. The purpose of this study was to measure the changes in cardiac output together with the renal hemodynamic and excretory responses to allow integrative determination of whether vasoconstriction likely accompanies the onset of type 1 diabetes. Rats were instrumented with a Transonic flow probe on the ascending aorta and with artery and vein catheters, and cardiac output and mean arterial pressure were measured continuously, 24 h/day, throughout the study. The induction of diabetes, by withdrawing intravenous insulin-replacement therapy in streptozotocin-treated rats, caused a progressive decrease in cardiac output that was 85 ± 5% of control levels by day 7. This was associated with significant increases in glomerular filtration rate, renal blood flow, and microalbuminuria as well as urinary fluid and sodium losses, with a negative cumulative sodium balance averaging 15.7 ± 1.6 meq by day 7. Restoring insulin-replacement therapy reversed the renal excretory responses but did not correct the negative sodium balance, yet cardiac output returned rapidly to control values. Increasing sodium intake during the diabetic and recovery periods also did not significantly affect the cardiac output response during any period. These results indicate that cardiac output decreases significantly at the onset of type 1 diabetes without glycaemic control, and although volume loss may contribute to this response, there also is a component that is not volume or sodium dependent. We suggest this may be due to vasoconstriction, but to what extent local blood flow autoregulation or active vasoconstriction may have mediated that response is not known.

peripheral vascular resistance; sodium excretion; thromboxane; angiotensin II

CARDIOVASCULAR COMPLICATIONS are a major cause of excessive morbidity and mortality in diabetes (10, 11, 15, 24, 31). They are manifested in some ways by alterations in the control of tissue blood flow and/or perfusion pressure (15, 22, 24, 27, 31), but the mechanisms underlying their development remain unclear. Glucose is known to have direct actions on renal and vascular tissue (8, 18, 26, 35), and progressive modification of renal and vascular structure and function could lead to secondary development of impaired blood flow and pressure control (13, 15, 21, 24, 27, 31). However, glucose also may have direct effects on those variables independent of its progressive effects on structure.

To test this hypothesis, we modified the streptozotocin (STZ) model of type I diabetes in rats to enable us to evaluate directly the effect of hyperglycemia on renal and cardiovascular function in the early stages of diabetes, before time has been allowed for development of structural changes. This model allows assessment of the responses to diabetic hyperglycemia immediately after initiation of the diabetic state while controlling for potential side effects of STZ. Continuous 24 h/day measurement of arterial pressure in this model previously revealed an effect of poor glycemic control to increase blood pressure that was rapid in onset, reversible, and repeatable (5). Those characteristics suggested a vasoconstrictor response to the onset of diabetes, and that was further evidenced by our subsequent measurement of a progressive, significant decrease in hindquarter blood flow over the first 6 days of diabetes that also was reversed rapidly (3).

However, the well-appreciated increase in renal blood flow associated with the induction of poor glycemic control in the early stages of diabetes did not lend credence to the vasoconstrictror postulate. Moreover, because there are marked changes in renal sodium and fluid handling as well, it was possible that the decrease in hindquarter blood flow observed in our previous study was solely the result of excessive volume loss. This study, therefore, was designed to measure the changes in cardiac output together with the renal hemodynamic and excretory responses to allow integrative determination of whether vasoconstriction likely accompanies the onset of type 1 diabetes.

METHODS
The experiments were conducted in 12 male Sprague-Dawley rats (~350 g; Harlan Sprague-Dawley, Madison, WI), and the protocols were approved by the Institutional Animal Care and Use Committee at the University of Mississippi Medical Center. Anesthesia was induced with pentobarbital sodium (50 mg/kg), the rats were intubated, and atropine was administered (40 µg/rat ip) to ensure an unobstructed airway. Under aseptic conditions, an artery catheter and a vein catheter were implanted as described previously (3–5). The

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rats then were connected to a rodent ventilator (Harvard Apparatus, Millis, MA), and anesthesia for the remaining surgery was maintained with isoflurane. Through an incision at the third intercostal space, a 3-mm Transonic (Transonic Systems, Ithaca, NY) flow probe was placed on the ascending aorta. All incisions were infiltrated with penicillin G procaine (300,000 U/ml) and bupivacaine (0.25%) at closure, and the flow probe leads and catheters were routed subcutaneously to the scapular region and exteriorized (3–5). After recovery from anesthesia, the rats were placed in individual metabolic cages, and the flow probe leads and catheters for each rat were passed through a stainless steel spring and connected, respectively, to an electrical swivel (Airflyte Electronics, Bayonne, NJ) and a dual-channel hydraulic swivel (Instech, Plymouth Meeting, PA) mounted in series above each cage.

The venous catheters were connected, via the hydraulic swivels, to a syringe pump (Harvard Apparatus) that ran continuously throughout the study. All solutions contained antibiotic (25,000 U penicillin G-rat−1·day−1) and were infused through a Millipore filter (0.22 μm, Cathivex; Millipore, Bedford, MA). The arterial catheters were filled with heparin solution (1,000 U/ml) and connected, also via the hydraulic swivels, to pressure transducers mounted on each cage for continuous measurement of arterial pressure. The flow probes were connected via the electrical swivels to Transonic model T101 flow meters (Transonic Systems (3)) for continuous measurement of cardiac output. The pulsatile flow signals from the flow meters and the amplified pulsatile arterial pressure signals were sent to an analog-to-digital converter and analyzed by computer using customized software. The analog signals were sampled at 500 samples/s for 4 s every 60 s continuously throughout the experiment.

**Sodium Intake**

Total sodium intake throughout the experiment was maintained constant at 3.5 mmol/day by continuous intravenous infusion of 22 ml/day sterile 0.9% saline combined with sodium-deficient rat chow (0.006 mmol sodium/g food; Teklad, Madison, WI). A sodium-deficient diet ensured that the daily sodium intake could be controlled at normal levels precisely by the infusion.

In addition, 9 ml of sterile water were added to the infusate; we have found that a total infusion volume of 31 ml/day greatly enhances the precision with which we are able to control glycemia with our insulin-replacement (IR) regimen. This infusion was begun immediately after placement of the rats in the metabolic cages.

**Experimental Protocol**

Group 1. Five to seven days were allowed for acclimation before control measurements were begun, and after a 4-day control period, STZ was administered (70 mg/kg iv). The following day, after determining the rats were hyperglycemic, IR was begun with a continuous intravenous infusion of regular insulin (porcine; Norvo Nordisk, Princeton, NJ) at 4 U/day by adding the insulin to the daily saline infusion. The insulin dose was titrated in each rat, based on daily blood glucose measurement, to maintain glycemic control for the next 7 days. We have demonstrated previously the ability of this method to maintain good glycemic control in STZ-treated rats (3, 5). After establishing normal, stable blood glucose concentrations, insulin was removed from the infusate to induce diabetes, and the diabetic period lasted 7 days. To control for potential time-dependent effects, the diabetic period was followed by a recovery period in which IR was begun again to restore good glycemic control. This is a powerful design because each animal serves as its own control.

Group 2: Effect of sodium intake. Sodium intake was clamped, as noted above, to enable more precise measurement of sodium balance. However, it is possible that the urinary sodium loss, and accompanying volume loss, associated with the diabetic period would confound the assessment of cardiac output control in rats that were unable to modulate their sodium intake. Therefore, the diabetic protocol was repeated in an identically prepared group of seven rats that were provided with sodium-replete chow ad libitum. The sodium-replete chow was Teklad's normal-sodium control diet for the sodium-deficient chow used in the clamped-intake rats, and it provided ~0.103 mmol sodium/g food.

In addition, the rats were provided with ~9 ml of sterile 0.9% saline/day such that total sodium intake during the control period was not different between groups. The volume of sterile water in this group was increased to 22 ml/day so that the total volume infused per day would equal the 31 ml/day infused in the sodium-damped rats.

Group 3: Measurement of urinary thromboxane and albumin excretion. Urinary thromboxane excretion was measured by assay of its stable metabolite, thromboxane B2, in the urine. This measurement required the addition of a variable volume of glycine buffer to the urine collection bottle to ensure urine pH was ~2.0. Because of the potential for this procedure to interfere with the ability to measure sodium excretion accurately, these measurements were made in a separate group of six rats instrumented and housed as the other rats but without the flow probe. They were maintained on the clamped sodium intake and subjected to the same experimental protocol as the other rats. Samples for albumin excretion were made from these rats on days preceding the thromboxane sample.

**Analytical Methods**

Blood glucose was measured daily during normal catheter flushing procedures: after clearing catheter dead space, 0.5 ml of arterial blood was withdrawn, and one drop was placed on a test strip of an Accucheck III blood glucose analyzer. The remainder of the blood was returned to the rat. Blood samples for the measurement of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), plasma insulin and protein concentrations, hematocrit, and plasma renin activity (PRA) were obtained during the control period on days 4, 5, or 6 during the first IR period (based on efficacy of glycemic control), day 4 of the diabetic period, and at the end of the second IR period; sample volume was 1.3 ml and was replaced by an equal volume of 0.9% saline.

GFR and ERPF were measured by calculating the clearance of 125I jodochloromc acid (Glofil) and 131I iodohippuran after 24-h infusion of the isotopes. Steady state is achieved with this procedure; therefore, a sample of the infusate was counted, and the infusion rate of isotope was substituted for urinary excretion rate of isotope to calculate clearance (2). Urine samples for measurement of thromboxane B2 were extracted on the day taken and were stored at ~30°C until RIA. Plasma insulin was measured using a Mercodia insulin ELISA kit (ALPCO, Windham, NH) with rat standards, and urine albumin was measured using a Neprath II rat albumin ELISA kit (Exocell, Philadelphia, PA). Urinary sodium and potassium concentrations were determined using ion-sensitive electrodes (Nova, Waltham, MA). Results are presented as means ± SE. Experimental data were compared with control data using ANOVA for repeated measures and Dunnett's test (6). Statistical significance was considered to be P < 0.05.
RESULTS

Blood glucose averaged $102 \pm 4$ mg/dl during the control period and increased to $383 \pm 30$ mg/dl after intravenous STZ administration (Fig. 1). IR maintained fasting blood glucose at an average of $62 \pm 3$ mg/dl over the next 6 days. In this experimental model, the intravenous insulin infusion rate is not varied overnight to account for increases in blood glucose likely associated with eating, and we have found that adjusting our insulin dose to maintain fasting blood glucose in the range of 60–80 mg/dl results in a 24-h sodium excretion that is very similar to pre-STZ levels. As shown in Fig. 2, urinary sodium excretion during the six IR days averaged $3.1 \pm 0.1$ meq/day compared with the $2.8 \pm 0.1$ meq/day average during the control period. Alternatively, we have shown that maintaining fasting blood glucose at control levels in STZ-treated rats in this model caused more disparity in sodium excretion after, vs. before, STZ, even though the difference was not statistically significant (5). Thus, although fasting glucose during IR in this study was significantly below control levels, the sodium excretion data suggest that 24-h glycemic control was more effective than if glucose was maintained at control levels.

All rats were given 4 U/day of regular insulin on day 1 post-STZ, and the insulin infusion dose ranged from an average of 4 to 3.4 U/day for an average value of $3.4 \pm 0.2$ U/day for the 6-day IR period. This yielded plasma insulin levels that were not different from control values (Table 1). Stopping the insulin infusion for the 7-day diabetic period decreased plasma insulin by $\sim 75\%$ (Table 1), and blood glucose increased on day 1 to $\sim 300$ mg/dl, with an average of $448 \pm 13$ mg/dl for the last 3 days of diabetes. The dose of insulin averaged $4.4 \pm 0.1$ U/day on the first day of the recovery IR period, and several rats received as much as 6 U/day on one or more days during the first three recovery IR days. We were able to decrease the dose as blood glucose approached the target range, and the insulin infusion rate on IR day 6 during recovery averaged $4.1 \pm 0.2$ U/day, with blood glucose averaging $87 \pm 12$ mg/dl.

Cardiac output tended to increase during the IR period after STZ administration (Fig. 3), and this was associated with a modest decrease in total peripheral resistance (Fig. 4), suggesting some vasodilatation may have occurred. The induction of diabetes, however, appeared to have been associated with vasoconstriction, because there was a significant, progressive decrease in cardiac output that was $85 \pm 5\%$ of control levels by day 7, and total peripheral resistance increased significantly by $27 \pm 10\%$ (Fig. 4). There was no significant change in mean arterial pressure in this study, although we have measured a significant increase previously during induction of diabetes (5). Cardiac output and total peripheral resistance returned to control levels with the restoration of glycemic control during the recovery IR period.

The hemodynamic changes suggest there was vasoconstriction during the diabetic period, but Fig. 3 also shows that the decrease in cardiac output was associated with a parallel decrease in cumulative sodium balance. Sodium balance was maintained during the IR period following transient natriuresis after STZ administration (Fig. 2), and the induction of diabetes caused progressive urinary sodium loss and a negative sodium balance of $15.7 \pm 1.6$ meq by day 7. Urine volume, which averaged $32 \pm 1$ ml/day during control and $49 \pm 4$ ml/day the last 3 IR days, was $>200$ ml/day the last 3 days of diabetes and averaged $218 \pm 7$ ml/day on day 7. Drinking also increased markedly, but the diuresis combined with the significant negative sodium balance provides strong evidence for volume depletion during the diabetic period, which is supported by the significant increases in hematocrit and plasma protein concentration that occurred, as well as by the significant increase in PRA (Table 1). However, in contrast to these parallel changes in cardiac output and sodium balance measured during the diabetic period, the two variables were dissociated during the IR recovery period. Thus

Fig. 1. Blood glucose in 12 rats measured one time during control period (C), day after streptozotocin (STZ) administration, then daily during control and recovery insulin-replacement (IR) periods, and diabetic (D) period. Values are means ± SE.

Fig. 2. Daily urinary sodium excretion in 12 rats in which sodium intake was clamped at approximately control levels throughout study. Values are means ± SE.
the rapid return of cardiac output to control levels was not accompanied by a similar change in sodium balance.

Figure 5 shows that the natriuresis during the diabetic period was associated with significant increases in GFR and renal plasma flow as well, and the urine excretory data from group 3 (Table 1) indicate that urinary albumin excretion also increased. Moreover, with restoration of glycemic control during the recovery IR period, GFR and albumin excretion returned to levels not different from control. The excretory data from group 3 also show that urinary thromboxane excretion increased nearly threefold during diabetes and was rapidly restored to control levels by a return to good glycemic control.

Effect of Sodium Intake

Because of the marked sodium loss associated with the diabetic period, it was necessary to test the effect of that change on the cardiac output response. Sodium intake during the control period averaged 3.5 ± 0.0 meq/day in the group with fixed sodium intake and 3.6 ± 0.1 meq/day in group 2 with ad libitum access to normal-sodium chow, and food intake averaged 20 ± 1 and 21 ± 1 g/day, respectively, in the two groups. Food intake changed in parallel in the two groups throughout the study, with significant, transient, decreases occurring on the day after STZ and for the first 2 days of the diabetic period, but with progressive increases during the remainder of diabetes. On day 7, food intake averaged 27 ± 2 and 30 ± 2 g/day in the fixed and variable sodium intake groups, respectively. Sodium

![Fig. 3. Cardiac output (A) and cumulative sodium (Na⁺) balance (B) in 12 rats in which sodium intake was clamped at approximately control levels throughout study. Values are means ± SE.](http://ajpendo.physiology.org/)

![Fig. 4. Total peripheral resistance (A) and mean arterial pressure (B) in 12 rats in which sodium intake was clamped at approximately control levels throughout study. Values are means ± SE.](http://ajpendo.physiology.org/)
intake in the fixed group increased from the control value of 3.5 ± 0.0 to 4.1 ± 0.0 meq/day by day 7 of diabetes. That change, although modest, was statistically significant and was due to sodium in the water because the food was sodium deficient, and water intake increased from an average of 17 ± 1 ml/day during the control period to an average of 162 ± 7 ml/day for the last 3 days of diabetes. In the variable-intake group, on the other hand, there was a significantly greater increase in sodium intake from 3.6 ± 0.1 to 5.3 ± 0.2 meq/day. This increase was nearly threefold greater than the increase in the fixed sodium intake group, and this significant difference between groups was due mainly to the salt in the food because water intake averaged 180 ± 12 ml/day in this group during the last 3 days of diabetes.

Despite the significant differences in sodium intake in the two groups, however, there were no significant differences in the changes in cardiac output during any experimental period (Fig. 6). Also, as in the group with fixed sodium intake, the return of cardiac output to control levels during the IR recovery period was dissociated from sodium handling. In the fixed-intake group, sodium intake remained relatively steady during the recovery period (actually returning to 3.6 ± 0 meq/day by IR day 6 as water intake normalized), and sodium balance remained significantly negative, whereas cardiac output returned progressively to control levels (Fig. 3). In the variable-intake group, however, sodium intake remained high during the recovery period, still averaging 5.0 ± 0.2 meq/day on IR day 6. This was due to continued elevations in food intake (which also occurred in the fixed-intake rats), but this significant difference in sodium intake during the recovery period had no significant effect on the change in cardiac output between the two groups.

DISCUSSION

These results show that the onset of diabetic hyperglycemia causes a significant and progressive decrease in cardiac output. The decrease appeared to be due in part to the significant renal fluid loss; however, there also is evidence that active vasoconstriction contributed to the decline. It is important to note that these changes can be ascribed to diabetic hyperglycemia per se, because they occurred before there was time for development of the vascular and glomerular injury that progress during the course of the disease. In addition, this study showed that at the earliest stages of diabetes there are significant increases in thromboxane production, renin secretion, and urinary albumin excretion, and all are rapidly corrected with restoration of glycemic control.

Natriuresis and diuresis are cardinal features of poor glycemic control in diabetes. In fact, urinary sodium excretion can provide an index of glycemic control integrated over a 24-h period, as we discussed relative to this model in METHODS. Thus it was possible that excessive volume loss could explain the decrease in blood flow we observed in the hindquarters in our previous study (3). This is supported by the remarkably parallel decreases in cardiac output and cumulative sodium balance measured in this study that also ap-

![Fig. 5. Glomerular filtration rate (GFR; filled bars) and effective renal plasma flow (ERPF; open bars) measured in 9 rats in which sodium intake was clamped at approximately control levels throughout study. Values are percent control values presented as means ± SE.](image)

![Fig. 6. Cardiac output in 12 rats in which sodium intake was clamped at approximately control levels throughout study (left ordinate; ■) and 7 rats with variable (and significantly greater) sodium intake (right ordinate; □). Values are means ± SE.](image)
pear to track well with the decrease in hindquarter flow previously measured (3). However, although the decreases in blood flow were associated closely with sodium loss during the diabetic period, cardiac output and sodium balance were dissociated during the recovery period. Thus the rapid recovery of cardiac output that occurred with no correction of the negative sodium balance suggested the presence of an underlying nonvolume component in the cardiac output responses. In addition, it is important to consider that the compensatory increases in salt and water intake that occurred during diabetes could be expected to blunt, or delay, the potential direct influence of urinary losses on cardiac output.

We routinely utilize a method of fixing sodium intake in studies of chronic arterial pressure and cardiac output control to prevent changes in intake from influencing our results and to allow for more precise measurement of sodium balance (4, 5). Using this technique in the present study, we were able to document a marked and progressive decrease in sodium balance that tracked right along with the decrease in cardiac output. However, an important physiological compensation for renal sodium loss is the stimulation of sodium appetite, and a response to diabetes is hyperphagia as well. Both should lead to an increase in sodium intake during periods of poor glycemic control, but, although the sodium-clamping protocol allowed ad libitum access to food, the food was sodium deficient, thus preventing sodium intake from increasing.

To quantify the effect of this on the decrease in cardiac output that occurred, we repeated the experiment in seven rats (group 2) in which a normal-sodium control chow was substituted for the sodium-deficient chow used in the sodium-clamped rats (details in METHODS). Despite significantly greater sodium intake during diabetes, however, the decrease in cardiac output was not different between groups (Fig. 6). This relationship also persisted in the IR recovery period, because sodium intake continued to increase the next several days in group 2 while actually decreasing in the other rats (due to normalization of water intake), yet there was no significant difference in the recovery of cardiac output between groups. Although close examination of Fig. 6 does suggest a tendency for a blunted decline in cardiac output and faster recovery in group 2, these observations suggest that cardiac output was not highly sensitive to, or totally dependent on, sodium and volume control.

Another possibility to explain the decrease in cardiac output is a direct effect of diabetes to impair myocardial function. Many studies have reported that measurement of various indexes of cardiac performance and contractility, in vivo (7, 19, 25) and in isolated hearts (28, 32, 33), indicate impaired cardiac function in diabetes. Interestingly, however, studies report that cardiac output either is decreased (25, 28, 32, 33) or increased (7, 14, 19, 20) in diabetes. Much of the discrepancy regarding cardiac output likely is due to the single-point determinations in those studies as well as to the different indirect methods used in intact animals, such as thermodilution or microspheres. In addition, the time after induction of diabetes and levels of glycemic control could have a major impact, and virtually all studies have evaluated cardiac performance many weeks, even years in human studies, after onset of diabetes. It is difficult, therefore, to extrapolate those results back to the effects of diabetic hyperglycemia immediately after onset, which was the time period in the present study, and it is important to emphasize that this is the only study to our knowledge to employ continuous, direct measurement of cardiac output 24 h/day in diabetes. In addition, in one in vitro study that did evaluate cardiac performance soon after onset, there was no impairment in the isolated working heart from 3-day diabetic rats studied with perfusate glucose concentration at diabetic plasma levels (23). Thus there is no direct evidence that impairment in myocardial function per se can explain the decrease in cardiac output measured at the onset of type 1 diabetes.

Because cardiac output is the sum of blood flow through all of the tissues in the body (12, 13), another explanation for the decrease measured in this study is that vasoconstriction occurred. Constriction of blood vessels in any tissue not only will decrease blood flow in that tissue but will, because of the consequent decrease in venous return, also decrease cardiac output (12, 13). The rapid return of cardiac output during the recovery period in this study, independent of changes in sodium balance, is consistent with the removal of a vasoconstrictor influence that developed during diabetes. The changes in total peripheral resistance also are consistent with this. The vasoconstriction, however, was not global, because renal plasma flow and GFR increased. Those changes are consistent with other reports (1, 29, 36) as well as with the parallel changes in urinary albumin excretion that reflect increased glomerular hydrostatic pressure (1). Considering our previous measurement of decreased hindquarter blood flow in this model (3), these data together suggest that skeletal muscle was a primary site of vasoconstriction.

The mechanism for the vasoconstriction, however, is not known. Glucose may have direct vasoconstrictor potential subsequent to increased de novo diacylglycerol formation (18) and many have reported impaired endothelial function in diabetes (30). The physiological relevance of the former mechanism in vivo, however, is not certain, and we have found no evidence for endothelial dysfunction at this early stage of diabetes (3). The increases in ANG II (as evidenced by the increase in PRA) and thromboxane that we measured could explain the vasoconstriction. The increase in thromboxane is consistent with other studies that have reported increased levels in diabetes (9, 34) and also is consistent with the rise in ANG II, which has been reported to stimulate thromboxane production (16, 37). Pharmacological blockade of those systems, however, will be necessary to determine their role in this model of diabetes. In addition, it is important to consider the role of tissue metabolic rate in determining the peripheral vascular and hence the cardiac output responses we
measured. Although vasoactive drugs and hormones can have significant, acute effects on tissue blood flow, these usually are short-lived, and tissue metabolic rate provides the primary driving force that regulates tissue blood flow (12, 13). Our previous measurement of decreased hindquarter blood flow (3) is consistent with other reports (14, 17) and with the possibility of a progressive decrease in skeletal muscle metabolic rate over the course of this diabetic period.

It remains unclear, therefore, to what extent local blood flow autoregulation or active vasoconstriction may have mediated the decrease in skeletal muscle blood flow. However, the results from this study suggest that selective regional vasoconstriction did accompany the onset of diabetes and contributed to the decrease in cardiac output independent of any effect of volume loss.

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REFERENCES

